Wang and Ma *Chinese Neurosurgical Journal* (2016) 2:29
DOI 10.1186/s41016-016-0047-2

Chinese Neurosurgical Journal

中华医学会神经外科学分会
CHINESE NEUROSURGICAL SOCIETY
中華醫學會
CHINESE MEDICAL ASSOCIATION

REVIEW Open Access

The diagnosis and management of hypothalamic hamartomas in children

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Abstract

Hypothalamic hamartoma (HH) is a rare developmental malformation often characterized by gelastic seizures. Recent advances in treating HH have led to dramatic improvements. However, clinical protocol of HH is poorly understood. Since 2002, department Pediatric Neurosurgery of Xinhua Hospital has maintained a multidisciplinary clinical program to evaluate and treat children with HH. This program has provided the opportunity to investigate the management of HH. In this review, we summarize the clinical progress and propose a clear management principle for different HH patients.

Keywords: Hypothalamic hamartoma, Gelastic seizures, Central precocious puberty, Electroencephalogram, Treatment

Background

Hypothalamic hamartomas (HH) are rare congenital malformations (1-2 /100 000 incidence) [1] located in the region of the tuber cinereum and third ventricle. This lesion is often associated with intractable seizures, cognitive impairment, behavioral disturbances and central precocious puberty. In fact, the manifestation of hypothalamic hamartoma is variant. Gelastic seizures as the hallmark are rare and are more likely to be diagnosed in early childhood. Patients later develop additional seizure types. The prevalence of epilepsy associated with hypothalamic hamartoma is estimated at 1 in 200,000 [2]. Recent functional MRI and intracranial electroencephalography (EEG) recordings have provided the proof that seizures originate in the hamartomas [3]. But some reports indicated another independent epileptogenesis [4], which is facilitated by the plethora of connections between the hypothalamus and the temporal-frontal lobe. On the other hand, gelastic seizures associated with HH are generally refractory to standard antiepileptic drugs as well as alternative therapies such as the ketogenic diet [5] and vagus nerve stimulation [6]. The detail of its mechanism and tailored treatment is still complicated issue. In the present review, we discuss the clinical characteristics and management of HH on the base of clinical experience and literature analysis.

Clinical presentation

Gelastic seizures GS

Gelastic seizures are usually present in childhood, even in the newborn period, and are manifested by frequent attacks of inappropriate laughter resulting from seizure activity. Gelastic epilepsy is characterized by recurrent brief seizures with initial laughter or grimacing. Without surgical intervention, most of gelastic seizures may progress to other seizure types such as tonic, myoclonic, or secondarily generalized seizures [7]. The association among hypothalamic hamartoma, central precocious puberty and gelastic seizures, has generated great interest since the time when Brening stall described the peculiar features of the syndrome [8, 9]. The intimate relationship with the mammillary body, fornix and mammillothalamic tract plays an important role in epileptogenesis associated with HHs [10–12]. The evolution of electroencephalogram (EEG) abnormalities, the development of generalized seizures years after onset of GS and the postoperative running down of interictal spike-wave and generalized seizures in patients may reflect secondary epileptogenesis [13]. More studies have demonstrated the intrinsic epileptic character of the hamartoma [14, 15], as well as the excellent outcome of cases where surgical removal was possible [16–18]. These data indicate that GS originates in the HH, and propagates to the

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hypothalamus and afterward to the neocortex. With the development of EEG and functional MRI, Someone reported that propagation of epileptic activity from the HH through the left fornix of the temporal lobe, and later through the cingulate fasciculus to the left frontal lobe [19]. The possibility of controlling seizures appears to In general, GS is pharmacoresistant and ends as a severe epileptic encephalopathy and catastrophic epilepsy of childhood [15, 20, 21]. The majority of patients with GS are male and present with a stalkless or sessile HH (Fig. 1), the majority of which distorted the third ventricle [22]. In the series of HH in Shanghai Xinhua hospital, 55 % (22/40) children only presented with progressive refractory epilepsy, including GS, tonic-clonic seizure and other complicated partial seizure. And further 22.5 % (9/40) demonstrated GS and CPP. Out of these 31 HHs with GS, 74.2 % (23/31) were male and 87.1 % (27/31) lesions were mainly involved in the third ventricle. Furthermore. Its effects are determined by functional connections with critical brain regions: the mammillary bodies to cause seizures [23] and the tuber cinereum or infundibulum to cause central precocious puberty CPP [24]. The cellular mechanisms responsible for seizure activity are always mysterious. Altered gamma-amino-butyric acid (GABA) function may contribute to epileptogenesis in animal models. Li indicated that neurons from the sample of HH demonstrate functional rundown of GABAR-mediated transmembrane currents in response to GABA agonist exposure [25]. Further research indicated that GABAA receptor-mediated excitation may contribute to seizure genesis in HH tissue [26].

Central precocious puberty CPP

The majority (86.4 %) of HHs in patients with isolated precocious puberty revealed a para-hypothalamic (Fig. 1b) position without touching the third ventricle [22, 27, 28]. Half of them were pedunculate and 40.9 % of the masses showed a diameter less than 10mm [22]. In our cases, the mean size of 40 lesions was measured at 18.6 ± 7.7mm;7 cases with simple CPP showed the mean size of lesions 14.9 ± 9.0mm and 28.5 % (2/7) of lesions demonstrated less than 10mm diameter in MRI. Interestingly, mean size 21.7 ± 5.2mm of 9 lesions presenting with CPP and GS was larger than these cases with simple CPP. Immunohistochemistry studies revealed the presence of GnRH-variant neurons in some HHs with CPP [29]. Hypothesis proposes that these neurons function as a heterotopic GnRH pulse-generator.

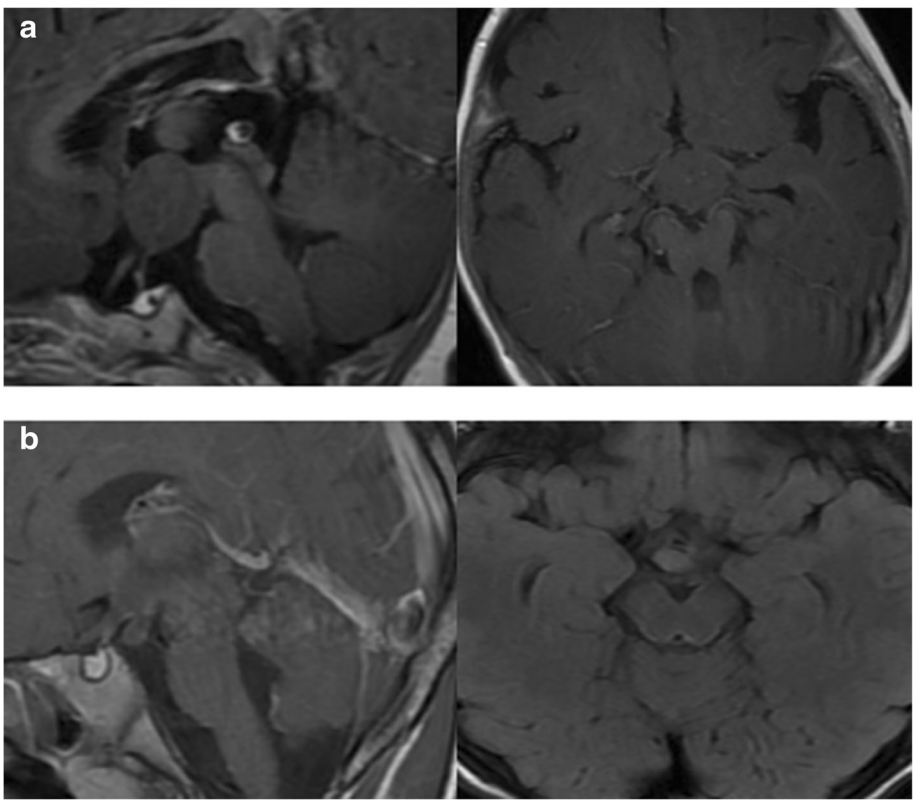

Fig. 1 **a** Sessile hypothalamic hamartoma, the mass allocates in the centre of Wills circle. **b** Pedunculated hypothalamic hamartoma, the patient with HH presented with single precocious puberty

However, in other cases related to CPP, GnRH immunoreactivity was absent. Furthermore, most of HHs with CPP contacted the infundibulum or tuber cinereum and were larger than those not associated with precocious puberty [24]. The pathogenesis of these alterations of the CPP remains unknown. Heike reported that two HHs with CPP contained astroglial cells. Pathological examination showed that HH was usually composed of an intermixed array of neurons, glia, and myelinated fibers [30]. These research implies that some HHs induce sexual precocity by activating endogenous LHRH secretion via glia-derived factors.

Cognitive malfunctions

In a series of cases, children with HH involving cortical association areas and the amygdala and hippocampus formation displayed cognitive deficits to vary extent [31, 32]. Almost half of the subjects had severe global memory deficits [33]. Both its severity and frequency in GS/complex partial seizure were related to cognizance. Ansgar suggested that more than half of the patients suffering from the GS of HH displayed deficits of cognitive functions such as visual and verbal learning and memory [33]. Another report described some patients of HH with cognitive deficit which includes 83.3 % oppositional defiant disorder and 75 % attention-deficit hyperactivity disorder [34]. The evaluation on cognitive abilities in patients with HH and GS report not only results on global intelligence quotient (IQ) performance but also other cognitive processes like attention or material-specific memory functions [35]. Furthermore, surgical resection is safe with a favorable outcome of epilepsy in 50 % with significant improvement in behavior and marginal change in cognitive functions. The reasons for thinking that HH with GS play a major role on development [36] and behavior lie in the following considerations. These children with HH usually have no history of retarded or abnormal development before the onset of GS. HHs in themselves do not apparently interfere with development and behavior. Children with HHs, but without epilepsy do not present cognitive and behavioral problems [9, 37]. Anatomical and functional imaging data in HH patients with GS do not identify dysplastic or brain malformations outside the hypothalamus [38]. Although the role of epilepsy severity is unclear, the number of antiepileptic drugs (AEDs) and neuroanatomical features of the HH lesion are recognized as being significantly related to patients' cognitive functions [32]. In fact, little is known about cognitive abilities in children with GS and HH, especially in the development of the preschool period.

Behavior disorder

Significant rates of aggression/hyperactivity in HH were noted, with 58 % of seizure patients meeting criteria for the affective subtype of aggression and 30.5 % having the predatory aggressive subtype. Some reported that behavioral problems, especially aggressive behavior, are accompanied by epileptic syndrome [1, 39]. The final proof of a direct functional role of epilepsy in cognitive and behavioral changes can only be shown with certainty when there is a marked improvement in these fields with successful surgical therapy of epilepsy. Nishio has noted improved behavior and cognitive functions when seizures were controlled with surgery [16]. Recent study echoed it. Refractory epilepsy related to behavioral and cognitive dysfunction may be the most common presentation of HH. Open surgical resection is safe with a favorable outcome of epilepsy in 50 % with significant improvement in behavior and marginal change in cognitive functions [36].

Examination of laboratory

MRI

A series of studies evaluated the use of brain MRI in the diagnosis of hypothalamic hamartomas [40]. In MRI, hypothalamic hamartomas were hyperintense on T2-weighted images (93 %) and hypointense on T1-weighted images (74 %); none of the lesions was enhanced by contrast; malformations of cortical development were infrequent [23]. Hippocampus sclerosis was hardly observed [39]. HH can be described according to the nature of its attachment (broad-based, sessile or pedunculate), its maximal diameter (<10 mm or ≥10 mm), growth characteristics (intra- or parahypothalamic) and the involvement of other brain structures (optic chiasm, infundibula stalk, the third ventricle). Para-hypothalamic growth was considered to be present if the HH was attached to the base of the hypothalamus either broad based or suspended by a peduncle, whereas an intra-hypothalamic hamartoma was defined as infiltrating the hypothalamic tissue. The pedunculate parahypothalamic type is generally associated with precocious puberty but is unaccompanied by seizures or developmental delay [22, 28]. According to our experiences, HH can be readily distinguished from normal hypothalamic gray and adjacent myelinated fiber tracts, best appreciated on thin T2-weighted images. Luo advised that HH consist of four categories based on MRI findings focused on the relationship between HH and hypothalamus or the third ventricle [41]. Furthermore, he suggested that the clinical manifestation is related to the topology of HH in relation to the hypothalamus. GS may be mostly presented in type III and rarely in type I. Recently, MRI is increasingly being employed as an adjunct to ultrasound, especially in a fetal brain. It allows for better visualization of in utero brain development and intracranial HH [42].

EEG

The scalp EEG is usually normal in children with GS. Video EEG was performed in some cases with unspecific findings. Interictal EEG was abnormal in 87.5 % patients with HH. Almost all HH with seizure were refractory to ADEs [43]. A few children with HH suffering from an epileptic progression usually show lateral focal slowing and epileptiform activity on the interictal EEG [44]. With the appearance of generalized seizures, the interictal EEG shows bilaterally synchronous and generalized epileptiform activity. The mechanism of this evolution is incompletely understood. Neocortical seizure propagation and secondary epileptogenesis are deemed to be significant. Several studies of HH children with GS have reported a restricted participation of neocortical areas in epileptic activity [45, 46], with epileptic spikes involving predominantly the frontal or temporal areas, most often in a single hemisphere [3]. Intra-hamartoma spikes and slow waves were detected on depth electrode recordings. In our cases, intra-hamartoma and interictal EEG was benefit for the understand for seizure propagation and epileptogenesis (Fig. 2). Clinical signature for appropriate resection of hypothalamic hamartoma was the disappearance of epileptic spikes in the cortical EEG. However,there is insufficient evidence that video EEG monitoring ultimately affects the outcome of patients with HH [47].

Pathology

HH tissues consist of well-differentiated neurons interspersed with glial cells. In related literature, all cases are composed of normal neurons and glia. However, there are different in the cytology and distribution of cells. Neuronal elements predominate in most cases, but a relative increase in astrocytic elements may be regarded with increasing age. In pathology, various sized nodular foci of neurons and areas of diffusely distributed neurons with interspersed glial cells are prevalent. Smaller neurons predominate, and most cases had only a few interspersed large ganglion cells. In a word, mature smaller neurons were the most prominent and most consistent histologic character of HH. Nodules of small neurons were an astonishing feature of the microarchitecture of HH lesions associated with epilepsy [30]. Qiu-pin found that various sized nodules of small neurons predominated with diffusely scattered small neurons and astrocytes between the nodules [48]. In other hands, Ben found that few solitary neurons can drive the development of GS and nodules of tiny neurons may not be a universal feature of HHs associated with epilepsy [49].

Approximately 5 % of HH cases are linked to Pallister-Hall syndrome (PHS). David identified a somatic chromosomal abnormality on chromosome 7p in a HH tissue sample. Resequence of GLI3 did identify loss of heterozygosity (LOH) within the GLI3 gene in the HH tissue samples. David indicated that the development of chromosomal abnormalities within GLI3 is associated with the pathogenesis of HH lesions in sporadic, non-syndromic patients with HH and intractable epilepsy [50].

Treatment

Sometimes, patients with gelastic seizures can be misunderstood as a risible baby, and accurate diagnosis of HH takes many years. There is a distinct difference in outcome and complications between patients treated for GS and those treated for CPP alone. Delayed treatment can exacerbate the development of cognitive and behavior disturbances. Unfortunately, there is a different side to the treatment of HH. When seizures are suspected, harm can also be done via invasive monitoring and inappropriate treatments, particularly surgery [51]. Recently, several surgical techniques can lead to a genuine reversal of the epileptic encephalopathy associated with HH. The decision-making process depends on the age, the size, it's anatomical feature, and the severity of epilepsy and the severity of cognitive/behavior comorbidity [52]. All in all, there are about three main surgical techniques being widely accepted by clinical doers.

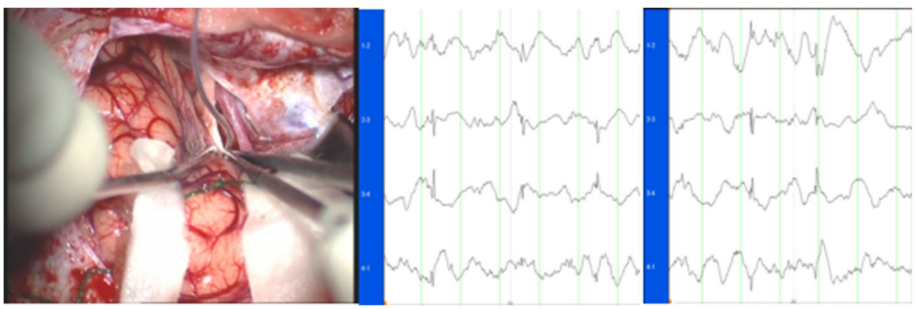

Fig. 2 In the process of lateral pterional approach for HH, we clinched a series of intra-hamartoma spikes and slow waves by an intra-hamartoma EEG in operation. The results directly guided us the degree of resection

Microsurgery

In appropriately selected patients, HHs can be removed completely or they can be completely disconnected from the hypothalamus as an acceptable risk [53]. It is possible to remove or disconnect the lesion from the adjacent hypothalamus in many patients without significant injury to the hypothalamus [54]. It is important to disconnect HH lesion from the mammillary body and the rest of the hypothalamus to achieve control of the seizures. In China, [55] Luo documented a series of six children with hypothalamic hamartoma-induced CPP who underwent microsurgical treatment. Significant prognostic factors for surgical outcome were HH size, surgical approach, and resection level. Patients with HH totally within the third ventricle have the best outcome from surgery [56]. All of them recovered completely to their age-appropriate state. Microsurgery is a great choice of treatment for pedunculate HH.

Surgical resection/disconnection of HH typically is taken into account when the associated seizures are refractory. No study was found that compared the seizure outcome between resection and disconnection. About operative techniques, the transcallosal anterior interforniceal approach to HH resection has been shown to be safe and to result in good seizure frequency reduction [57]. The transcallosal anterior transseptal interforniceal technique is an effective and relatively safe technique when used for the resection of HH [58]. This operative approach is applicable to other pathology in the hypothalamic region and has advantages compared with the standard transcallosal approach to the third ventricle [59]. Recently, Jacqueline documented that approach to HH resection is associated with a high risk of long-term memory impairment in older adolescents [57]. Charles compared three surgical approaches [52]: one lateral pterional, another midline frontal through the lamina terminals and a third transcallosal interforniceal approach. A disconnection procedure, usually lateral pterional, aims to disconnect the lesion without the risks of major resection. The transcallosal interforniceal approach is the most successful with 69 % of patients seizure-free. Iman reviewed [60] his reports and related literatures. Their lesions were approached from above through a transcallosal anterior interforniceal approach in six, endoscopically through the foramen of Monro in one, and from below with a frontotemporal craniotomy including an orbitozygomatic osteotomy in three. Sessile lesions are best approached from above. Approaches from below adequately expose pedunculate HHs. The likelihood of curing seizures appears to be higher when lesions are approached from above rather than from below. Of course, those patients with both intrahypothalamic and parahypothalamic components may require approaches from above and below. For appropriately selected patients, the success of controlling seizures with an orbitozygomatic (OZ) pterional surgery is comparable to results utilizing transcallosal or transventricular approaches [61]. Currently, the traditional effective surgical route appears to be the transcallosal anterior interforniceal approach [62]. There is a question for complicating HH: The different partial resection of lesions based on separate approach of microsurgery showed a similar outcome of controlling seizures in literature. In the center of the author, most of the patients were received lateral pterional microsurgery. And half of these patients still suffered from diverse epilepsy, comprehensive effect of which was less to the one reported in previous HH literature. However, Four patients underwent endoscopic resection of transcallosal anterior transseptal interforniceal technique. Out of these patients, three patients were protected from severe seizures. Surgical complications included thalamic infarct, visual deficits, diabetes insipidus short-term memory impairment, and hydrocephalus.

Endoscopy

Although HH can be controlled by microsurgical resection of the lesion, excision of deep-seated lesions is often associated with morbidity and mortality. Endoscopic disconnection is less invasive and seems to be well suited for a similar indication. Endoscopic disconnection appears to be a very safe way to treat hamartomas in intraventricular locations [63]. Joong-Uhn advocated the endoscopic disconnection surgery as a safe and effective treatment for HH-related epilepsy by blocking the spread of epileptic discharges from the lesion [64]. There is increasing evidence that removal or disconnection of HH can lead to seizure control and improvement in behavior. Shim suggests [65] that HH-related seizures may be controlled by blocking the seizure propagation from epileptogenic HHs through simple disconnection, regardless of the treatment modality. Ng YT evaluated the efficacy of endoscopic resection of HHs and compared the seizure outcome with a prior reported transcallosal approach. Forty-nine percent were seizure-free, and 71 % had a more than 90 % decreases in seizure frequency. After comparison endoscopic resection with the transcallosal approach, the authors did not find any significant difference in seizure outcome [66]. Recently, new case reports showed that endoscopic disconnection of HH resulted in rapid resolution of neurological symptomatology [67]. In fact, some cases of author echoed the advance: minimally invasive endoscopic surgery for HHs may represent an effective alternative to the open procedures.

Radiosurgery: GKS and SRT

Jean Régis indicated that gamma knife surgery (GKS) is as effective as microsurgical resection and safer [68].

GKS also allows avoiding the vascular risk related to radiofrequency lesion or stimulation. Adib [69] showed that GKS was associated with few complications and about 60 % seizure-free rate as part of a multimodal treatment protocol. Another 30 % of patients experienced an astonishing improvement (Engel Class III) after GKS. In 2000, Régis reported a series of 8 patients, with 50 % cases attaining Engel Class I by GKS. The data were updated in 2006 to include more than 60 patients who had undergone GKS [68]. Some doctors suggested that resection of epilepsy-related HHs may be replaced by disconnection procedures. Their results confirm disconnection procedure feasible and acceptable morbidity, and particularly good seizure outcome in patients with intraventricularly located HHs [70]. A stereotactic surgical plan was devised to disconnect the HH from the hypothalamus, medial forebrain bundle and dorsal longitudinal fasciculus [71]. Seizure frequency was reduced from several seizures per day to less than one tonic-clonic seizure during sleep per month. The disadvantage of radiosurgery is its delayed action [68]. The immediate effect on sub-clinical discharges turns out to play a major role in the dramatic improvement of sleep quality, behavior, and developmental learning acceleration at school. Recently, some centers introduced that stereotactic laser ablation (SLA) is a minimally invasive approach to the treatment of medication-resistant epilepsy. SLA minimizes the neurocognitive and endocrine adverse effects of open surgery [72]. The evaluation and safety of radiosurgery in children are still at multifaceted observation.

In China, some documents suggested that stereotactic radiofrequency thermocoagulation (SRT) may be an effective and safe treatment option in selected cases of HHGS [73]. Transient central hyperthermia, hypertension, and tachycardia were observed during the coagulation procedure. No gelastic seizure was induced by deep stimulation. Central hyperthermia and postoperative fever after stereotactic thermocoagulation occurred more frequently compared to using the open approach, the disadvantages of stereotactic radiofrequency thermocoagulation are acceptable. Kameyama suggested [74] that the present SRT procedure has favorable efficacy and invasiveness and has no adaptive limitations. Recent reports are [75] showed that SRT provided minimal invasiveness and excellent seizure outcomes even in patients with giant HHs. Repeat SRT is prudent for residual GS. SRT is a single feasible surgical strategy for HH regardless of the tumor's size or shape.SRT should therefore be considered before adulthood.

Conclusion

Hypothalamic hamartoma is a nonneoplastic heterotopic mass of normal nervous tissue. Its usual manifestations include gelastic seizure, central precocious puberty and cognitive malfunctions due to AEDs and epileptic encephalopathy. The clinical presentations of HHs and option of treatment may base on its anatomy. Magnetic Resonance Imaging investigation is mandatory in its diagnosis although EEG is lack of its specificity. Neurosurgery plays the most important role in its treatment and endoscopic disconnection of HHs is a promising choice with safety and validity.

Abbreviations

CPP, central precocious puberty; EEG, electroencephalogram; GS, Gelastic seizures; HH, hypothalamic hamartoma

Acknowledgement

Not applicable.

Funding

This work was supported by grants from the National Key Basic Research Program, (NKBRP 2010CB945203), the National Natural Science Foundation of China (81271382); Clinical Trials of Xinhua hospital (Shanghai Jiao Tong University 2015LC12).

Availability of data and materials

Not applicable.

Authors' contributions

BW drafted the manuscript. JM conceived of the study, and helped to draft the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

Received: 22 March 2016 Accepted: 27 July 2016
Published online: 18 September 2016

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