■ Clinical commentary

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# The Moro reflex: insights into the pathophysiology of generalized tonic-clonic seizures and infantile spasms

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**ABSTRACT**

The Moro reflex (MR) is a primitive reflex that disappears after the first three months of life. It was described by the Austrian paediatrician Ernst Moro (1874–1951) in 1918, although the earliest visual representation of the MR dates back to the first half of the 14th Century, in a fresco by Ambrogio Lorenzetti (1290-1348). The neural centre underlying the MR is located in the lower part of the brainstem since it can be elicited also in anencephalic infants, as shown by the Austrian neurologist Eduard Gamper (1887-1938) in the first medical description of anencephaly (1926). The MR is due to the activation of an archaic neural circuit present in the newborn, the activity of which is later inhibited by the upper brain structures. Given their semiological resemblance, epileptic spasms and generalized tonic-clonic seizures might be due (at least partly) to the pathological activation of the same neural archaic circuit involved in the genesis of the MR. The neuronal network underlying these different phenomena might be located in the pons. In these seizure types, the activation of the same neural circuitry involved in the MR could occur through either direct excitation or through an indirect "liberating" mechanism, secondary to epileptic disruption of cortical inhibitory control on subcortical structures. The movements of the upper extremities in epileptic spasms, in the initial phase of generalized tonic-clonic seizures, and the MR might involve a distinct neural circuitry, which is (or becomes) hyperexcitable as a consequence of a pathological condition (epilepsy) or physiological brain immaturity (the MR).

**Key words:** generalized tonic-clonic seizures, history of neurology, infantile spasms, Moro reflex, pathophysiology

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On 7th May, 1918, giving a lecture entitled "Das erste Trimenon" (The first trimester [of life]), the Austrian paediatrician, Ernst Moro (1874–1951), described the behavioural phenomenon that came to bear his name: "If a young infant is placed on the examination table and one hits the pillow on either side with the hands, both arms move apart symmetrically and then converge with slightly tonic arch-like movements. At the same time, the legs show a similar motor behaviour" [1].

Emphasizing the final arch-like adduction of the arms, Moro called this phenomenon "Umklammerungreflex" (embracing or clasping reflex), suggesting – in analogy with the behaviour of newborn apes – that it was a behavioural pattern allowing infants to clasp their mothers [2]. However, it was later recognized that the main component of the Moro reflex (MR) is the abduction

and extensions of the arms, rather than their adduction [2-4] (*supplementary figure 1, video 1*). Furthermore, the extension and abduction of the legs are not always present [2], and motor responses of the lower limbs are widely variable [5].

The MR is a primitive reflex that disappears after the first three months of life and is still routinely elicited to evaluate the neurological status of the infant (although adopting the head dropping method [6]). It is a normal phenomenon, not associated with any neurological or EEG abnormalities. The neural centre underlying the MR is located in the lower part of the brainstem. This is demonstrated by the fact that it can be elicited also in anencephalic infants, as shown by the Austrian neurologist Eduard Gamper (1887-1938) in the first medical description of anencephaly (a condition that was initially termed after him as "Gampersches Mittelhirnwesen") [7] (*supplementary figure 1*) and in subsequent reports [5,8]. As such, the MR is a behavioural phenomenon distinct from the startle reaction [5, 8], which is due to the activation of an archaic neural circuit present in the newborn, the activity of which is later inhibited by the upper brain structures [5], similar to other reflexes present in infants, such as the "toe phenomenon" (Babinski reflex) [9].

To the best of our knowledge, the earliest visual representation of the MR dates back to the first half of the 14$^{th}$ Century. In the "Madonna and Child enthroned with Saints", a fresco painted by Ambrogio Lorenzetti (1290-1348) and preserved in the St. Augustine Church in Siena, Italy, the posture of the infant, Jesus, strongly resembles that of the MR (*supplementary figure 2*). Although it might also represent a startle reflex [10], the absence of flexion of legs points towards a MR, here depicted as a reaction of the Christ Child to the unexpected loud chirping of a bird in front of him (a goldfinch; a traditional symbol of Jesus' passion and death) [11]. As shown in this painting, the MR could represent an "alarm response" triggered when an excess of information reaches one or more of the infant's senses (*e.g.*, when perceiving a sudden head movement, a loud sound, or a bright light) [10].

It is not widely known that Ernst Moro himself, together with Berta Asal, coined the term "Blitz-Nick und Salaam Krämpfe" to indicate infantile spasms [12]. In some patients with developmental and epileptic encephalopathies, infantile spasms can persist during adulthood, maintaining the same semiological and electroencephalographic features [13]. Epileptic spasms are seizures characterized by muscle contractions, mainly affecting the axial musculature, involving flexor (35%), extensor (20%), or mixed flexor/extensor (45%) muscles. Sometimes they consist of abduction of the arms in a "salaam" posture [14]. Epileptic spasms usually last 1-2 seconds and therefore have a duration that is intermediate between myoclonic jerks (which last milliseconds) and tonic seizures (which last > 2 seconds). Of note, the bilateral proximal massive movements of epileptic spasms are sometimes reminiscent of the symmetrical extension and abduction movements observed with the MR [15-19], particularly in the case of extensor epileptic spasms (*video 2*). Interestingly, it has been hypothesized that the same brainstem circuitry is involved in the generation of both phenomena [17, 18]. However, as shown in a detailed video-polygraphic study, epileptic spasms are characterized by a complex pattern of muscular activation, which despite clinical similarity, is markedly heterogeneous and difficult to explain in terms of cortical or reticular generators [20]. Furthermore, the heterogeneous pattern of muscular recruitment and the disproportionately long latencies found in epileptic spasms (as with the MR) are not compatible with a "startle-reflex" pattern [21].

It is perhaps even more intriguing to consider the similarities between the MR and the initial phase of generalized tonic-clonic seizures (*video 3*); at seizure onset, the arms are elevated, abducted, and externally rotated with the palms facing forward, with a posture similar to that associated with the response to the command "put up your hands!" [22]. However, unlike the MR, where arm flexion at the elbows occurs after arm extension [23], in generalized tonic-clonic seizures, the elbows are semi-flexed from the onset.

Given their semiological resemblance, it is tempting to speculate that both epileptic spasms and generalized tonic-clonic seizures might be due (at least partly) to the pathological activation of the same neural archaic circuit involved in the genesis of the MR. The neuronal network underlying these different phenomena might be located in the brainstem, more specifically in the pons. The MR can be elicited in anencephalic newborns with an intact rostral pons and is also present in infants under light sedation [7, 8]. Furthermore, clinical and experimental studies have shown that the grasp reflex inhibits the MR, confirming that this phenomenon is mediated through the brainstem [8], and requires the integrity of the pons and the vestibular nuclei [24], whereas the spinal cord has no role in its generation [5]. Similarly, studies in animal models have demonstrated that the pontine reticular formation is crucial in the generation and expression of tonic convulsions, as bilateral lesions of the pontine tegmentum involving the superior cerebellar peduncles and the nucleus reticularis pontis oralis can attenuate the tonic components of generalized seizures, without effect on clonus [25]. Similarly, it has been hypothesized that a functional disturbance of the pontine tegmentum plays a role in the pathophysiology of infantile spasms [26]. In these seizure types, the activation of the same neural

circuitry involved in the MR could occur through either direct excitation or through an indirect "liberating" mechanism, secondary to epileptic disruption of cortical inhibitory control on subcortical structures [18, 27]. The movements of the upper extremities observed in epileptic spasms, in the initial phase of generalized tonic-clonic seizures, and in the MR might involve a distinct neural circuitry, which is (or becomes) hyperexcitable as a consequence of a pathological condition (epilepsy) or physiological brain immaturity (the MR).

In this case, the motor phenomena would therefore represent the activation of subcortical central pattern generators, which are thought to play a role in the genesis of several automatic behaviours observed during epileptic seizures and parasomnias. Central pattern generators are genetically determined neuronal circuits in the brainstem and spinal cord, which are responsible for stereotyped innate motor behaviours essential for survival (*e.g.*, feeding, locomotion, reproduction, *etc.*) [28, 29]. In higher primates, these central pattern generators are largely under neocortical control, and their activation explains the similar stereotyped motor phenomena encountered in epileptic seizures, parasomnias [28, 29], syncope [30], and even movements associated with brain death [31]. Interestingly, the concept of central pattern generators resembles the hierarchical and almost "geological" view of the nervous system and its functioning proposed by John Hughlings Jackson (1835-1911) [32]. The British neurologist, one of the founders of modern epileptology, believed that the central nervous system was made up of several structures superimposed on each other like geological strata, with upper neuronal centres suppressing (*i.e.*, inhibiting) the function of the lower ones. Hence, transient dysfunction or damage to the upper layers could release and unmask the function of lower neuronal structures. A similar hierarchical concept of the central nervous system and its function would explain the re-emergence of primitive reflexes or motor patterns in certain neurological conditions (*e.g.*, the Babinski sign or the triple flexion reflex after pyramidal tract dysfunction [33, 34]).

More than one hundred years after its first description, the MR continues to fascinate and stimulate discussion, and its features could shed further light on the pathophysiology of epileptic seizures. The semiological resemblance between epileptic spasms, generalized tonic-clonic seizures, and the MR might be due (at least partly) to the pathological activation of the same neural archaic circuit. However, as fascinating as they might be, our considerations regarding the similarities between these different phenomena remain speculative. Further studies are warranted to analyse the neural substrates of the MR and its relationship with epileptic seizures. ■

**Supplementary material.**
Supplementary data and summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

**Disclosures.**
Francesco Brigo and Alessandro Porro have no conflicts of interest. Eugen Trinka reports personal fees from EVER Pharma, Marinus, Angelini, Arvelle Therapeutics, Argenix, Medtronic, Bial-Portela & C, NewBridge, GL Pharma, GlaxoSmithKline, Boehringer Ingelheim, LivaNova, Eisai, Epilog, UCB Pharma, Biogen, Genzyme Sanofi, Takeda, and Actavis outside the submitted work.

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## Legends for video sequences

### Video sequence 1.

The Moro reflex evoked in a seven-week-old healthy infant. The sudden loss of head support leads to a massive movement of abduction and slight elevation of the arms, which is the primary component of the reflex. The subsequent component of adduction of the arms can be lacking, as in the present case. The MR is shown twice, first at normal speed and then in slow motion.

### Video sequence 2.

Adult with epileptic spasms. Arms are suddenly elevated and abducted with abrupt flexion at the elbows and of the neck. The abduction and elevation of the arms are similar to the proximal movements seen in the first component of the MR, whereas the semi-flexed elbows from the very onset of the seizure are a different feature. In the patient shown in this video, unlike the MR elicited in a healthy infant where the head remains fixed and the limbs move symmetrically, the head and eyes turn to one side (left) with the left leg being markedly extended and abducted. A movement of extension and abduction of the legs, similar to that exhibited by this patient, can also occur inconsistently during the MR. The epileptic spasm is shown twice, first at normal speed and then in slow motion.

**Video sequence 3.**

Adult with primary generalized (clonic)-tonic-clonic seizure. At the onset of the seizure, the arms are suddenly elevated and abducted with flexion at the elbows and palms facing forward. The abduction and elevation of the arms are reminiscent of the proximal movements seen in the first component of the MR (and in epileptic spasms). However, unlike the MR (in which arm flexion at the elbows can occur after arm extension), at the onset of generalized tonic-clonic seizures, the elbows are semi-flexed. The flexion of the legs is a further feature that is not typical of the MR. The seizure is shown twice, first at normal speed and then in slow motion.

**Key words for video research on www.epilepticdisorders.com**
*Phenomenology:* non-epileptic paroxysmal event (*video 1*), spasm (epileptic) (*video 2*) generalized (*video 3*), tonic-clonic seizure (*video 3*)
*Localization:* not applicable (*video 1*), unknown (*video 2*), generalized (*video 3*)
*Syndrome:* not applicable (*video 1*), west syndrome (*video 2*), idiopathic generalized not specified (*video 3*)
*Aetiology*: not applicable (video 1), unknown (videos 2 and 3)

## TEST YOURSELF

**(1) The Moro reflex:**
A. is a primitive reflex that disappears after the first three months of life
B. is a pathological reflex indicating pyramidal tract dysfunction
C. is elicited by stroking along the lateral border of the foot sole
D. is a type of epileptic seizure seen only in newborns and infants

**(2) Infantile spasms and the initial tonic phase of generalized tonic-clonic seizures:**
A. are the same type of epileptic seizure, occurring at different ages
B. are a subtype of Moro reflex
C. might arise following the pathological activation of the same neural archaic circuit involved in the Moro reflex
D. should be distinguished from the Moro reflex

**(3) The considerations regarding the similarities between infantile spasms, the initial tonic phase of generalized tonic-clonic seizures, and the Moro reflex:**
A. remain speculative
B. could shed further light on the pathophysiology of epileptic seizures
C. should be supported by further studies to analyse the neural substrates of the Moro reflex and its relationship with epileptic seizures
D. all of the above

*Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.*