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## History of neurology

# A history of oculogyric crises during the encephalitis lethargica pandemic

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### ABSTRACT

A pandemic of what came to be known as encephalitis lethargica spread starting in the winter of 1916–1917 and continued into the 1930s. Neurological after-effects, namely permanent parkinsonian syndromes and various abnormal movements, permanently disabled the survivors of the one or two million victims, often children or young adults. Among them, a small proportion developed a symptom that was little known up to that point and that is currently exceptional: oculogyric crises; that is, a lateralised, dystonic upward movement of the eyes known as a tonic eye fit. This paper proposes a history of the recognition of this symptom, its inclusion in the neurological nosography, and the pathophysiological hypotheses postulated a century ago.

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A century ago, at a time when the world was facing a severe pandemic, the so-called Spanish flu, a second pandemic emerged simultaneously, that of encephalitis lethargica [1]. Previously, sporadic cases seem to have occurred. But the disorder had been largely forgotten before the pandemic [2].

On 1 April 1917, René Cruchet of Bordeaux (1875–1959), on staff at the Bar-le-Duc neuropsychiatric centre, presented a paper to the Medical Society of the Hospitals in Paris covering forty cases of subacute encephalomyelitis observed over a period of nine months; these represented 3% of the war wounded and sick patients he had examined. The paper was published on 27 April 1917 with two famous co-authors, François Moutier (1881–1961), a student of Pierre Marie (1853–1940) at La Salpêtrière hospital, and Albert Calmette (1863–1933), a bacteriologist at the Institut Pasteur [3].

Then on 17 April 1917, Constantin von Economo (1876–1931), a Viennese neurologist, presented a paper at the Society of Psychiatry and Neurology of Vienna, describing seven cases of a new form of encephalitis that he had identified and named “encephalitis lethargica”. His observations were published on 10 May 1917 in the journal *Wiener klinische Wochenschrift* [4]. Credit is due to von Economo alone for being the first to perform an accurate microscopic anatomopathological examination. The name given by von Economo was legitimately adopted around the world, much to Cruchet's chagrin. He continued to use the term “diffuse encephalomyelitis”. British authors spoke of “epidemic stupor”. Jean Lhermitte (1877–1959) proposed “primitive ophthalmoplegic encephalitis with narcolepsy” or “primary poliomesocephalitis with narcolepsy” [5,6]. Indeed, the hallmarks of this encephalitis were

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oculogyric paralysis accompanied by ptosis, hypersomnia, fever, and a rapid change in the general condition, progressing often over very long periods and leading to improvement with neurological after-effects or, in 25–35% of cases, to death [7,8].

In the postencephalitic phase of the disease, these effects had an impact on nearly all survivors; a distinction could be made between permanent and paroxysmal manifestations. A Parkinsonian syndrome was the most frequent of the irreversible after-effects [9]. A chronic visual disturbance suggested retrospectively the diagnosis of encephalitis, especially in mild forms. The characteristic oculomotor symptom was deficient ocular convergence during upward movement of the eyes.

There were also pupillary disturbances: anisocoria or deficient reaction to light or to accommodation. Ocular paralysis and nystagmus were rare [10]. Although oculogyric crises only occurred in 20% of patients with postencephalitic parkinsonism, this paroxysmal episodic manifestation, became an almost pathognomonic sign. As a terminological issue, these crises were described around 1920: oculogyric crises as “crises oculogyres” in French, in German as “Schauanfalle”. Oculogyric tonic spasms were called in French, “spasmes toniques oculogyres”; in German, “tonische Blickkrämpfe,” or tonic eye fits. The Swiss neurologist Robert Bing (1878–1956) of Basel and the French Leonhard Schwartz (1885–1948), a student of Pierre Janet (1859–1947), proposed “vertical oculogyric crises of postencephalic parkinsonism”, which was too long to be commonly used. These authors underscored the paroxysmal nature of these crises to distinguish them from “athetotic, choreic, or myoclonic hyperkinesia that can be observed in disorders of the striatum independent of the specific aetiology (cf. encephalitis lethargica)” [10].

When the encephalitis and these oculogyric crises emerged, the differential diagnoses were tuberculous meningitis, tubercle of the cerebellum, and brain tumour. Lumbar puncture showed cerebrospinal fluid to be more or less normal, making it possible to eliminate these diagnostic hypotheses. Some also mentioned Magendie-Hertwig syndrome (skew deviation) [11], looking for a cerebellar or vestibular lesion [12].

## 1. What is an oculogyric crisis?

Without a prodrome, or only a trembling of the eyelids or blepharospasm, “the eyes suddenly deviate, most often upward, hidden under the upper eyelid which is itself retracted. The patient tries repeatedly to lower their eyes and sometimes adopts a compensatory position of the head” [13], according to Georges Guillain (1876–1961) and Pierre Mollaret (1898–1987). This oculogyric crisis is sometimes also called a “tonic eye fit” (Figs. 1 and 2). Physical exertion, emotions, and peripheral excitation (tickling) may trigger the crisis which lasts a few seconds to several hours. Guillain and Mollaret noted a similarity between these crises and the fixed stare in Parkinson’s patients which they called “ocular bradykinesia”. At the height of the crisis, the eyeball seems irreversibly blocked and blinking is suspended, resulting in a



**Fig. 1 – Oculocephalogyric crisis observed by G. Marinesco and reported by S.-E. Jelliffe in 1932 [49] (BIUsanté, Université de Paris).**

kind of ocular catatonia. Sometimes the lateralisation of this tonic position of the eyeballs suddenly reverses. Throughout the crisis, parkinsonian rigidity significantly increases, often accompanied by akinetic mutism; that is, the motor incapacity to form sounds [14]. Indeed, several of the symptoms have a catatonic quality.

After a variable time, the eyeball is suddenly unstuck from its position, following exterior excitation, for example, or inhalation of amyl nitrate. Sleep or an intravenous injection of hyoscine (IV scopolamine 0.5 mg), an atropine derivative, or even a placebo, ends the crisis. Natural sleep, rather than sleep induced by barbiturates, is the safest way to bring it to a close. Ill-advised attempts to inject pilocarpine and especially eserine, which Jules Tinel (1879–1952) made experimentally in his research on the role of the autonomic nervous system [15], worsen this tonic spasm; the derivatives of atropine, having an inverse effect, put an end to it [16]. Sometimes the movements of the eyeball are jerking, resulting in an “ocular cogwheel” effect as described by Camillo Negro (1861–1927) in 1922 [17], a phenomenon that may have been confused with nystagmus.

In addition to this dystonic form, there are tonic-clonic forms in which the eyeballs undergo a series of large rhythmical jerks, involving one or more conjugate movements of the eyes. Then the eyes remain in one position for several minutes.

A painful sensation of the eye being torn out of its orbit is frequent. Examination reveals anisocoria. The patient, often diplopic, experiences violent anxiety; some patients have been driven to suicide [18]. Holding the eyelid closed, when possible, provides immediate relief. A deviation of the head, sometimes of the head and trunk, is frequent, resulting in an oculocephalogyric crisis (Figs. 3 and 4). The repetition of the crises does not follow any pattern, from a single crisis to the existence of crises recurring every ten minutes for several hours.

During the oculogyric crisis, the parkinsonian symptoms increase: open mouth, sialorrhoea, anarthria, and shaking, while the patient remains fully conscious, indicating the absence of a functional cortical deficit. However, the patient seems indifferent to his or her surroundings, as if in a state of

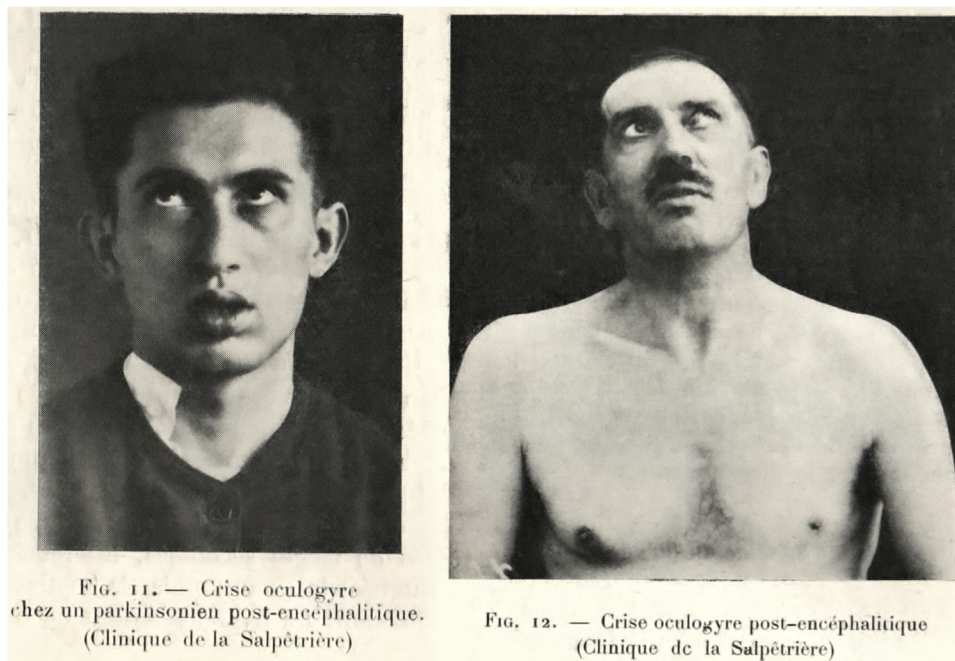


Fig. 2 – Patients of G. Guillain and P. Mollaret in 1932 [13] (OW collection).

apathy with anxiety; others have the impression of being invaded with obsessional thoughts which they vainly try to dispel (e.g. arithmomania) [19].

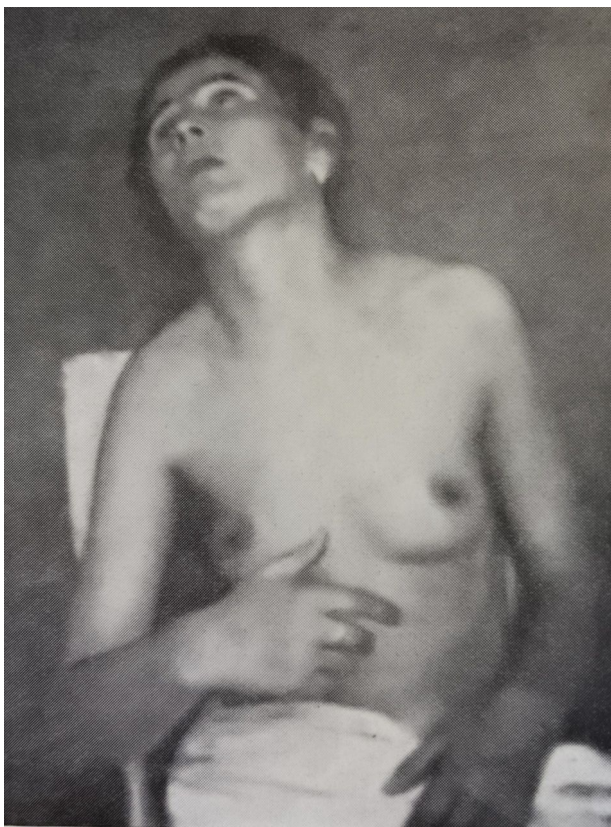


Fig. 3 – Oculocephalogyric crisis observed by G. Marinesco and A. Radovici [23] (BIUsanté, Université de Paris).

The general examination always reveals acceleration of cardiac and respiratory frequency, exaggerated oculo-cardiac reflex, non-systematised modifications of labyrinthine reactions, and various vasomotor and secretory disorders (sialorrhea). Once the fit is terminated, these various parameters return to normal.

These crises occur mainly in young people between 10 and 30 years of age. It is notable that the lateralisation of the eyes is toward the side of the body exhibiting the stronger parkinsonian hypertonia.



Fig. 4 – Oculocephalogyric crisis observed by P.K. McCowan and L.C. Cook [45] (BIUsanté, Université de Paris).

In terms of timing, as isolated events these spectacular manifestations happen one to eight years (exceptionally fifteen to twenty years [20]) after the acute period of encephalitis; more frequently they may occur at or after the onset of parkinsonian syndrome. In 1926, Gottlieb August Wimmer (1872–1937) professor of psychiatry in Copenhagen, reported the case of a girl with a parkinsonian syndrome of four years' duration who had an oculo-ogyric crisis that inaugurated a relapse of lethargic somnolence [21]. Once they appear, the crises recur sporadically throughout the patient's life and never totally disappear [22]. Most of the time, the crises take on a pattern specific to the patient: daily with a circadian cycle, weekly on the same day, etc.

The patient's entourage often observes a depressive mood in the days that precede the crisis, making it possible to predict the onset. Some authors highlight the associated psychological elements, such as volition or the effect of suggestion as a trigger, a phenomenon that may be related to unblocking a "freezing" effect in response to an order. Similarly, the observation of contagious crises resulting in a sort of epidemic has led some authors to consider them as hysterical manifestations even though there is no doubt about their organicity [23]. Abdol-Hosseini Mir-Sepassy (1907–?), originally from Teheran and a student of Jules Froment (1878–1946) of Lyon, made hysteria and oculo-ogyric crises the subject of his 1935 thesis [24].

Within this vast grouping, "the ocular aspect is only one part, undoubtedly the most visible and strange, of a complex paroxysmal state" [25] according to René Delbeke (1881–1953) and Ludo von Bogaert (1897–1989), who used hypnosis to stop the crises. They attributed their triggering to psychic influences mainly, having observed cases of contagion [26].

## 2. Inclusion of oculo-ogyric crises in the nosography of encephalitis lethargica

During the session on 13 February 1920 of the Medical Society of the Hospitals in Paris, Victor Morax (1866–1935) and Jacques Bollack (1883–1951) highlighted the frequency of associated ocular movement disturbances compared to the rarity of real ophthalmoplegia [27] during the acute phase of encephalitis. They did not mention oculo-ogyric crises. Demonstrating that these crises were little known (noticed), Louis Dor (1866–1954), an ophthalmologist from Lyon, did not mention them in his general review in 1920 [28]. Nor did Yvette Dautrevaux (1892–?) in her 1920 thesis [29] or Désiré Houin (1896–1974) in his 1922 thesis in Nancy [30].

Rudolph Stähelin of Basel is considered the first to have described these crises in March 1920 [31]. Giovanni Cavina of Bologna published the first Italian case, also in 1920 [32]. Arrigo Frigerio in Florence gave the curious name of "opisthotonos" to the tonic eye fits of a child [33]. In both cases, the crises appeared two years after the acute phase of the disease.

Wilhelm Oeckinghaus (1869–1950) of Greifswald described this type of crisis in 1921 without naming it. In March 1920, he treated a 15-year-old girl who had experienced lethargy in December 1919. She presented with a parkinsonian syndrome and anxiety about the repeated nature of the crises: "Both eyeballs roll slowly upwards, involuntarily and in concert, to

such a degree that only the lower edge of the iris remains visible, and she bent her head well backwards, in order to escape being compelled to gaze upwards" [34].

The ophthalmologist Constantin Pascheff (1873–1961) of Sofia saw his first case in 1924, but reported having heard similar complaints by patients since 1920 [35]. He spoke of a tic due to the "associated periodic deviation of the eyes upward" accompanied by what patients deemed to be visual hallucinations.

Gabrielle Lévy (1886–1934), a brilliant student of Pierre Marie (1853–1940) at La Salpêtrière hospital [36], was one of the first to describe "clonic crises of the eyeball and the upper eyelid" in her remarkable 1922 thesis [37]. Observation number 47 describes a 13-year-old girl examined two years after an episode of prolonged somnolence and one year after developing a complete parkinsonian syndrome. Fifteen days before the consultation, she experienced five minutes of "an upward roll of the eyeballs which moved 'every which way,' making it impossible to return to a normal position". Observation 52 reports on an 18-year-old girl with a parkinsonian syndrome. Lévy witnessed a crisis: "The eyeballs are suddenly rolled under the upper eye lid, then undergo violent, rhythmic, nystagmic jerking in the vertical direction. The terrified patient then begins to cry, saying she is afraid of going blind. All voluntary downward or lateral movements of the eyeball are impossible. However, she is able to see, though her vision is blurred. When she is ordered to close her eyes during the crisis, she does so but incompletely, and the eyelids blink in time with the jerks. She can easily re-open them". Lévy did not provide any specific pathophysiological commentary; she named the crises "ocular crises".

In 1923, Jules Euzière (1882–1971), André Blouquier de Claret (1867–1940), and Paul Pagès of Montpellier coined the terms "anoblepsia", for the upward spasm, and "catoblepsia", for the downward spasm [38]. At the same time in Italy, M. La Torre published a summary article on encephalitis, notably its after-effects, intended for his compatriots. Of his twelve personal cases, the second developed typical oculo-ogyric crises [39].

The psychiatrist António de Sousa Magalhães e Lemos (1855–1931) in Porto described the first Portuguese case in 1924. An 18-year-old man with typical encephalitis lethargica developed a parkinsonian syndrome made worse by dystonic claudication of the left leg with clubfoot: "During claudication in our parkinsonian patient, we sometimes observed a conjugated movement of the head and eyes to the left. his eyes rolled up under the upper eyelids and outward; he remained in this position for ten minutes. We were going to photograph him but then the muscles suddenly released and the disturbance suddenly disappeared. His head returned to its normal position and the patient laughed, moving his eyes in all directions". Often this deviation of the head and eyes was accompanied by contraction in the masseters and an inability to swallow. As this patient also had writer's cramp, he had dystonia at three sites, simultaneously or separately. Magalhães e Lemos attributed the same pathophysiology to these three localisations of muscle tone disturbance, namely a functional defect in the striatum [40].

In 1925, he psychiatrist Leslie Benjamin Hohman (1891–1972) at Johns Hopkins University described the first four cases

in the United States. A bus driver had to stop driving due to involuntary tonic eye fits. No matter how hard he tried, he could not prevent the occurrence nor stop the crises which lasted several hours, several times a week. A 26-year-old nurse experienced depression, stiffness, and slowing; simultaneously, four times a week, her eyes rolled upward for two hours. A 31-year-old man developed a parkinsonian syndrome in addition to personality changes, producing fits of anger and short-temperedness, when "his eyes got up in the air and he couldn't get them down". Finally, during the lethargic phase another man of the same age developed episodes of dystonia in a lower limb, sometimes accompanied by "spasms" of the eyes upward and to the left [41].

In 1925, Gottfried Ewald (1888–1963) in Erlangen considered himself the first to describe oculogyric crises [42]. We have seen that he was wrong, but his text included instructive photos for his German readers.

Mary Ribson Barkas (1889–1959), originally from New Zealand - the first woman psychiatrist to work at Bethlem Psychiatric Hospital in London-, described the first English case in 1926 [43]. Profiling a female patient in distress, she wrote that her eyes "moved up and to left, became fixed, could be brought down by volitional effort, but soon returned to the position of the spasm". The parkinsonian syndrome only appeared a few weeks after the oculogyric crises, accompanied by a depressive state; this differed from the other cases where the crises occurred once the parkinsonian syndrome had set in.

The epidemic also affected China starting in 1919, notably a number of students in Hong Kong, as reported by M.O. Pfister in 1926. Pfister reported five cases of "compulsory fixation of the eyeballs" [44].

P.K. McCowan and L.C. Cook, psychiatrists at Whitchurch Hospital in Cardiff (Wales), observed their first case in 1923. In 1928, 17% of their patients hospitalised for the after-effects of encephalitis presented with oculogyric crises that appeared in all of them more than a month after onset of the parkinsonian syndrome [45].

In a 1928 review of the literature for the journal *Brain*, the Scottish neurologist Edwin Bramwell (1873–1952) asserted that oculogyric crises were pathognomonic for the existence of an after-effect parkinsonian syndrome, particularly when this syndrome was mild [46].

In a summary article reviewing all the ocular disturbances encountered during the encephalitis epidemic, A. Michael Critchley in Bristol wrote in 1928: "Oculo-gyral crises (Tonic Eye Fits) are of immense interest and the theories as to their pathogenesis have caused considerable controversy. The crises consist in a spasmodic conjugate deviation of the eyes usually in an upward direction, coming in paroxysms and lasting for a period varying from a few seconds to hours. They are often accompanied by, or rather are part of generalised convulsions. These attacks are a late complication of epidemic encephalitis and are not common". Some of his patients complained of visual hallucinations which they recognised as such. For him, the crisis ended with deep sleep. After mentioning a striatal origin, Critchley laid out his own theory. "Although there is no known cortical centre subserving upward ocular deviation, nevertheless a cortical nidus is well known, which, on stimulation, will evoke deviation of the eyes

in a lateral direction. One can conceive the lateral oculogyral crises as resulting from stimulation of such a centre [...]. One can therefore picture these encephalitic oculogyral crises as the result of impulses arising in a previously diseased cortical centre for the representation of eye movements" [47].

The psychiatrist Erwin Wexberg (1889–1957), an Austrian émigré practising in New Orleans after 1934, described the complex symptomatology, a mix of psychiatric symptoms (compulsions) and neurological symptoms (ocular motricity); one could "rearrange certain hitherto well-established ideas in neurology as well as in psychopathology". He considered oculogyric crises much more frequent than previous estimations of around 20% of cases of encephalitis after-effects: "Patients rarely talk spontaneously about their ocular attacks, surely because of the fact that their spontaneous mental activity as a whole is considerably impaired" [48].

In 1932, the psychiatrist-psychoanalyst Smith Ely Jelliffe (1866–1945) published a book on his interpretation of the psychopathology of oculogyric crises, based on a vast review of the international literature that summarised all the publications about these crises [49]. For him, they were always associated with affective disturbances, mainly an obsessional and compulsive state as revealed by testimony from patients who ruminated on ideas during tonic eye fits.

### 3. Pathogenic theories

Von Economo's encephalitis lethargica initiated the study of behavioural consequences of subcortical disturbances induced by a supposed viral infection. The acute manifestations, highly variable, included extrapyramidal disturbances, myoclonia, ocular movement disorders, paralysis, psychosis, mood swings, sleep inversion, and catatonia. These main pathological changes implicated the substantia nigra, globus pallidus, and hypothalamus (blocked striatum dopamine receptors). For those that survived beyond the acute phase, a symptom-free recovery period was often followed by postencephalitic disturbances, parkinsonism in adults and behaviour problems in children. The appearance of depression, mania, obsessive-compulsive disorder, and hyperactivity in postencephalitic patients led, at the time, to consideration of the role of the basal ganglia in mood regulation, personality, and obsessive syndromes [50].

Retrospective analysis of encephalitis lethargica cases has established parallels with the secondary effects of neuroleptics. Like neuroleptics, encephalitis produces a continuum of cognitive problems ranging from emotional indifference to apathy to a waking stupor. It also generates similar acute dyskinesia: akinesia, akathisia, dystonia, oculogyric crises, and tremor. Chronic motor and cognitive disturbances, like those associated with neuroleptics, are tardive. The initial acute phase of encephalitis lethargica also parallels neuroleptic malignant syndrome. Dysfunction in the basal ganglia may explain the after-effects of encephalitis and the tardive effects of neuroleptics [51].

As a psycho-organic phenomenon occurring as an after-effect of epidemic encephalitis, of which the ocular aspect is the spectacular objective element, the oculogyric crisis was

the subject of numerous theories; those that received the most attention are discussed below.

The corticopyramidal theory likens the oculogyric crisis to Jacksonian epilepsy (partial seizure) which appears to be caused by the discharge of the centre for conjugate deviation of the head and eyes [52]. Wladyslaw Sterling (1877–1943) in Warsaw referred to extrapyramidal epilepsy in 1924 [53]. However, oculogyric crises differ from the ocular movements that may be observed during grand mal seizures.

Jean-Alexandre Barré (1880–1967) and his student Louis Reys defended a labyrinthine theory based on the observation of a change in vestibular excitability during the crisis. The crisis was believed to liberate a vestibular subcortical centre normally inhibited by the pallidum [54].

McCowan and Cook asserted in 1928 that these symptoms reflected the impaired cortical inhibition of subcortical structures<sup>45</sup>. Similarly, for Delbeke and van Bogaert, “oculogyric crises are a precursor and the most remarkable symptom of an extensive and mixed state of inhibition that is similar to the states of catalepsy and sleep” [26]. They referred to a “complex cramp”.

The psychiatrist Benno Slotopolsky (1897–1980) interpreted the oculogyric crisis as a pathological modification of the phenomenon of sleep, drawing a parallel with the ocular movements occurring in sleep [55].

The strong emotional reactions during the crises have led psychiatrists to various interpretations. In several publications, Smith E. Jelliffe argued that these crises are linked to psychoaffective disorders and have a functional origin [56,57]. Georges Marinesco (1864–1938) and Anghel Radovici (1886–1956) of Bucharest also established a link between oculogyric crises and pithiatism (hysteria), as described by Joseph Babiński (1857–1932), based on three criteria: crisis after an emotion, reproduction by suggestion, and disappearance by persuasion. They associated them with damage to autonomic centres of the hypothalamus (infundibulo-tuberian region) and “the central nuclei”, seeming to situate the origin of hysteria in these areas [23]. Raoul Mourgue (1886–1950) had a similar idea, interpreting the crisis as a narcissistic regression in those with a parkinsonian syndrome as adults who had been victims of trauma in childhood [58]. Many psychoanalysts upheld these interpretations into the 1960s, like the interpretations they developed to explain tics and dystonia.

In 1924, August Wimmer wrote the first book exclusively about the chronic after-effects of encephalitis lethargica [59]. He highlighted the contrast between parkinsonian hypertonia and “hyperkinesia”; that is, dystonia as illustrated by the oculogyric crisis. For him, the neostriatum was the origin of the disturbance after a pathological stimulation originating in the cerebellum, where he believed the causal lesion to be.

Bing and Schwartz viewed these crises as the indication of “release phenomena (Enthemmung syndrome); The pallidal segment of the striatum continuously receives centripetal impulses by the pathway of association neurons that link it to the large relay station of general sensitivity; that is, the thalamopallidal fibres. The inhibition exercised by the putaminocaudate segment prevents the energy accumulated in the paleostriatum from discharging. This may occur, either in a disorderly way (but more or less continuously as chorea or athetosis), or in a paroxysmal way, as tics heterogeneous in

their localisations but with quite a few common criteria. If the moderating function of the neostriatum is lacking, the patient may present some form of these automatic movements originating in the subcortex” [10].

Ewald observed that eye coordination was intact; thus, the origin of the disturbance could only be supranuclear. However, at that time the physiology of movement was not yet perfectly understood. In 1920, Charles Sauvinau (1862–1924), a student of Henri Parinaud (1844–1905), used his observations of patients with disturbances in ocular movement coordination to confirm his personal theory of supranuclear coordinating centres which remained, nonetheless, approximative [60]. According to him, there were “lesions in the grey matter in the walls of the aqueduct of Sylvius, the walls of the third and fourth ventricles, and part of the corpora quadrigemina”.

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#### 4. Conclusion

A century after the emergence of this pandemic, its aetiology remains unknown. After eliminating a toxic origin (botulism), authors writing at the time most often subscribed to the idea of viral infection, but lacked the means to prove it. The fact that this pandemic and the so-called Spanish flu were simultaneous supported this theory even though no virus was recognised as causing the parkinsonian syndrome. The current hypothesis centres on a post-infectious, auto-immune encephalitis primarily affecting the basal ganglia [61]. More specifically, antibodies against NMDA receptors might explain the symptomatology [62]. Sporadic cases of encephalitis, resembling the numerous cases that appeared a century ago, are published from time to time; about 200 such cases have been reported since 1940. For example, Howard and Lees described, in 1987, four cases presenting parkinsonian syndrome, oculogyric crises, akinetic mutism, and obsessive-compulsive behaviour [63]. But what aetiopathogenic link can be established between encephalitis and parkinsonian syndrome? One of the approximations noted by numerous authors involves the diagnosis of encephalitis, which at the time was only established by a clinical picture that varied greatly from one case to another. This is why Hoffman and Vilensky recently proposed rigorous criteria for diagnosing encephalitis lethargica that would enable reliable comparative studies, notably of chronic after-effects syndromes and modern auto-immune treatments [64]. Whereas patients a century ago did not have any effective treatments, in our day and age the chronic after-effects justify using DOPA therapy, which has proven effective [65].

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#### Statement of ethics

This work required no approval from an institutional review board and was prepared in accordance with ethical guidelines of the journal.

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The author declare that he has no competing interest.

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