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Breaking Down Myasthenic Crisis

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Myasthenia gravis may not be known to the patient before fulminant worsening of swallowing and breathing occurs. Respiratory weakness has reportedly appeared without prior diagnosis, but the absence of some prior signs is improbable. Myasthenia gravis does not proceed in a steady downhill course; instead, it progresses with stops and starts until, at some point, it requires close monitoring in an intensive care unit. There is a general understanding that myasthenia gravis becomes a "crisis" once airway or respiratory support is needed. Experts in treatment of myasthenia gravis have struggled with the definition of rapid, potentially deadly myasthenic worsening. The late Kermit Osserman, one of the most prominent clinicians with an experience of over 1200 cases, devoted a full chapter to it in his 1958 book *Myasthenia Gravis* and titled it "crisis" and cemented the different types into medical vernacular [1]. Historical review of these cases allows us to examine the semiotics of the crisis in detail.

Bulbar Paralysis and Secretions

Myasthenia gravis has been present for centuries and mostly undiagnosed. Viets traced the first description of these cases back to the observations of Thomas Willis in *De Anima Brutorum* nearly 350 years ago [2].

Myasthenia gravis—and its potential for critical worsening—entered the diagnostic minds of British (and American) physicians after the manuscript by Campbell and Bramwell in *Brain* [3] (Fig. 1). Both added nine cases to cases already published in the "German textbooks on neurology" (Fig. 1). Their paper offers detailed descriptions of 60 patients, of which 23 were fatal. The frequent involvement of bulbar muscles in their cases led them to name the phenomenon "asthenic bulbar paralysis." Ptosis was common and bothersome because the compensation of "throwing back the head" was impaired by weakness of the neck muscles. The paper emphasized choking, fluid regurgitation through the nose, diminished palatal reflex, and a lowered tone of voice suggesting weakness of the vocal cord adductors. Additionally, patients were unable to thrust out the cheek and maintain protrusion of the tongue. When chest movements were measured circumferentially, the difference between inspiration and expiration did not exceed a quarter of an inch. Dyspnea with exertion was common as well as "unaccountable attacks of breathlessness, during which the patient is in danger." Sputum accumulation in the mouth accompanied these dyspneic attacks with patients unable to swallow or to spit it out. "The tongue appears to sink back into the mouth." Pulling back the tongue markedly improved the symptoms. The fatal cases were a result of choking or "dyspneic attacks" or "dyspneic attacks with pneumonia." (Autopsies found nothing anatomically wrong in the medulla oblongata.) The paper emphasized that "involvement of respiratory muscles with consequent attacks of dyspnea is a symptom of gravest significance" and warned that death may occur during one of these attacks.

Later, in a notable article, Rowland reported 39 fatal cases that occurred between 1930 and 1955 [4]. He urged the physician to watch for premonitory attacks of respiratory distress, use sedatives cautiously, initiate early mechanical ventilation, and control for infection.

Crisis? What Kind of Crisis?

Already in 1945, H. R. Viets, another world-renowned expert in myasthenia gravis, reported 60 cases from Massachusetts General Hospital, and his experience was regularly updated in the literature by others. Viets described myasthenia gravis as a disease characterized by "easy fatigability of the voluntary muscles" [5, 6]. In 1946, Viets wrote, "In our Clinic, patients are furnished with ampules of neostigmine methyl sulfate (0.5 mg) when severe symptoms develop; two ampules should be given to an adult, either subcutaneously or intramuscularly. A hypodermic needle may be used. Any qualified person can give the drug to the patient." He added that some deaths could have been avoided with early treatment. In one of the patient examples, "The dysphagia was promptly

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Critical Digest.

MYASTHENIA GRAVIS.

BY

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THE disease known as myasthenia gravis has hitherto attracted little attention in this country. Nevertheless some sixty cases have been recorded within the last few years, chiefly by German writers, and the disease has found a recognised place in German text-books on neurology.

We have ourselves had the opportunity of examining nine cases.

The disease has received various names. The earlier cases were published as "cases of bulbar paralysis without discoverable anatomical changes," and some recent writers have adopted this nomenclature. Strümpell introduced the term "Asthenic bulbar palsy." The affection is, however, not confined to the bulbar muscles. Other names which have been employed are "general profound myasthenia," "Erb's disease," the "Erb-Goldflam" and the "Hoppe-Goldflam-symptom-complex." Jolly has proposed the term "myasthenia gravis pseudo-paralytica," and this, or for short "myasthenia gravis," appears to us the most suitable and convenient hitherto suggested.

SALIENT FEATURES OF THE DISEASE.

There is weakness, sometimes amounting to complete paralysis, of some or all of the voluntary muscles. After prolonged rest of the affected muscles, *e.g.*, the first thing in the morning, they may respond normally to the will, but

Fig. 1 Campbell and Bramwell's seminal paper published in *Brain* (1900). Used with permission

relieved by a diagnostic ampule of neostigmine, and swallowing reflexes, studied with barium under fluoroscopy, became normal within 20 min of the injection."

But others cautioned against this approach because over-dosage with neostigmine could lead to gross toxicity with dyspnea, choking, frothy saliva, a sense of constriction in the chest, pallor, perspiration, and muscular fasciculations. The mechanisms of neostigmine toxicity could be a result of its curariform effect and muscular collapse, which, when mistaken for under-dosage, lead to further injection of the drug and further worsening.

Bedlack and Sanders further refined the definition of crisis as "weakness from acquired myasthenia gravis that is severe enough to necessitate intubation or to delay extubation beyond 24 h after surgery." They suggested counting repeated intubations as separate crises "if there is a clear period of stable improvement (lasting at least 24 h) between them." They proposed defining crisis incidence as the "number of confirmed myasthenic crises in a specified period of observation; and divided by number of MG patient-years in the period of observation" [7].

"Crisis" was mentioned in several reviews but was not part of the commonly used Osserman classification. (Group 3 was defined as "acute severe myasthenia gravis developing over a period of weeks to months with severe bulbar involvement often needing tracheostomy and respirator" [1]). Osserman defined it as either under- or over-treatment of anticholinesterase drugs—the myasthenic or cholinergic crisis [1, 8]. This was a totally new concept in 1953, several years after Mestinon (pyridostigmine bromide) became available and about 20 years after the use of Prostigmin (neostigmine bromine). There were differences of opinion; many felt under-dosing was more common than overdosing [9] and vice versa [10]. Overdosing with Prostigmin would cause a curare effect.

Rowland was among the first to point out the dangers to patients of this overdose; he noted that large amounts do not improve weakness and may even provoke additional weakness in previously unaffected muscles. Too much acetylcholine induces a neuromuscular-depolarizing block (nicotine effect) with consequently more weakness. Muscarinic effects come first with sweating and "eructation" followed by abdominal cramps, increased peristalsis, vomiting, and dyspnea. Subsequently, nicotine-like effects occur with generalized weakness and fasciculations that appear initially in the eyelids and facial muscles before becoming more generalized. There is also anxiety, restlessness, giddiness, tremors, and emotional lability. The degree of weakness occurring in the two crises is often identical, but the excessive salivation, marked sweating, clammy and cold skin, muscular fasciculations would support the diagnosis. On the other hand, in a 1951 paper, Rider described a patient in myasthenic crisis showing dyspnea, weakness, and much mucous and saliva. This resulted in the patient choking on increased secretions and requiring 336 mg of IM neostigmine over 24 h [11].

Osserman suggested a tensilon test (now abandoned) to differentiate the two crises. In his book, he noted an 18% risk of crisis, mostly myasthenic, but up to a third were cholinergic [1]. Crisis occurred most frequently occurred in the first 2 years of the disease. The ratio of myasthenic crises to cholinergic crises was three to one. Tracheostomy greatly facilitated management of excessive bronchial secretions, particularly in cholinergic crisis, and usually shortened the overall time spent on the respirator (Fig. 2). Of the 24 crises that terminated in death, 15 were myasthenic, 5 were cholinergic, and 4 were mixed in nature [1].Treatment of cholinergic crisis was atropine sulfate, often in large doses but starting with 1 mg. Atropine dose could exceed 8 mg but was stopped when the pupils started to dilate.

Randt was the first to recommend acute withdrawal of all anticholinergic medication and placement in a ventilator [12]. The main reason was that the drug contributed to a full NMJ block and secretions as a result of the parasympathetic effects of Prostigmin. However, the remissions were of short duration and required the patients to start medication in reduced doses. Patients not responding to several doses of neostigmine methyl sulfate, 2 mg, given deep subcutaneously (or those showing obvious signs of neostigmine intoxication and not responding to reduction in dosage, with inability to maintain proper pulmonary ventilation) could be precipitously withdrawn from neostigmine and placed in the respirator after elective tracheotomy. The rationale for this therapy was fourfold: (1) neostigmine was demonstrated ineffective in

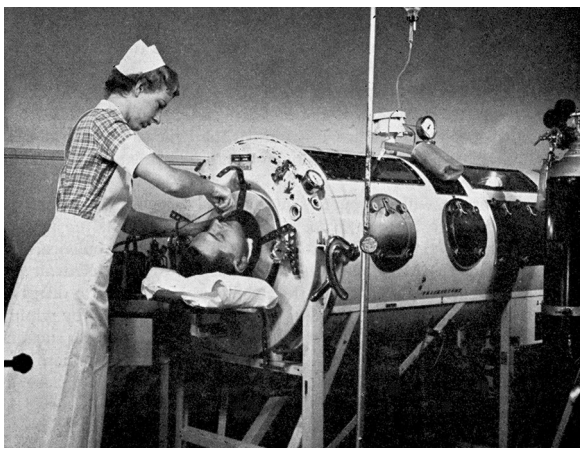

Fig. 2 Iron-lung treatment in myasthenic crisis. Used with permission from Osserman's book

maintaining vital respiratory function; (2) the drug contributed to further neuromuscular junction block; (3) the parasympatheticomimetic properties of neostigmine enhance pharyngeal and tracheobronchial secretions, which, in turn, promote the development of atelectasis and pneumonia; and (4) minimal response may produce respiratory movements and breathing out of phase with the respirator, which is counterproductive because it leads to further exhaustion. The main pathophysiologic mechanisms were clarified by Osserman's group [13] (Fig. 3).

Later Studies

Cohen and colleagues analyzed the outcome of myasthenic crises between 1960 and 1980 at the Neurological Institute Columbia-Presbyterian Medical Center [14]. (By 1962, patients were being placed on positive-pressure

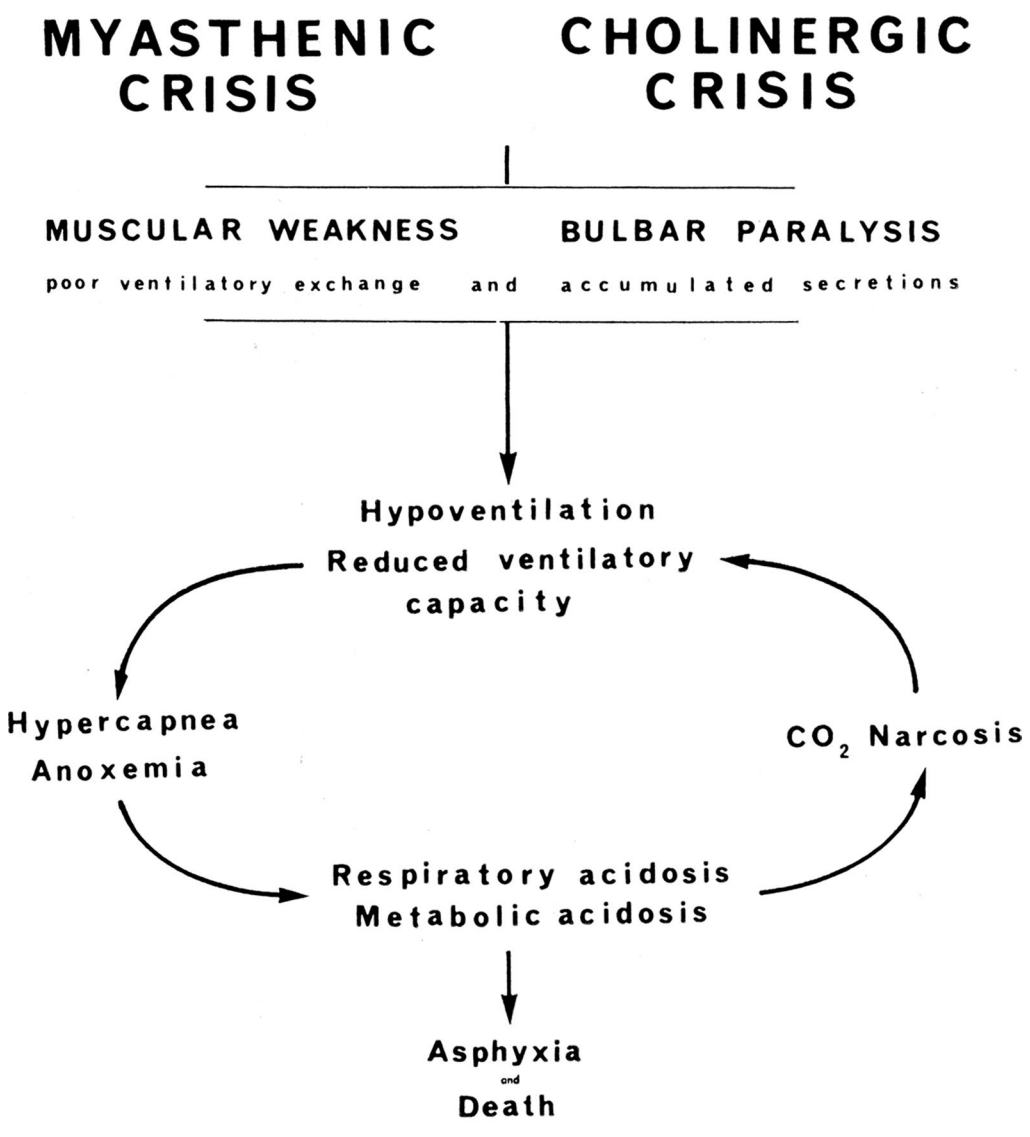

Fig. 1.—Respiratory pathophysiology of crisis in myasthenia gravis.

Fig. 3 Respiratory pathophysiology of crisis in myasthenia gravis and effect of tracheostomy with controlled ventilation on the respiratory physiology of crisis. *From* Blaugrund et al., L.I.V. Studies in myasthenia gravis: the role of tracheotomy and controlled ventilation. Ann Otol Rhinol Laryngol 1964;73(3):618–31 [13]. Used with permission

ventilators.) Their policy was to continue anticholinergic drugs while on the ventilator. The incidence of crisis remained constant over 2 decades at 16% but with a mortality of 33% in the 1970s. The median onset of myasthenia and first crisis was 21 months but could occur as early as 1 month and as late as 27 years after diagnosis. The median duration of respiratory support was 2 weeks but could range from several hours to 1 year. Most patients received a tracheostomy [14].

Conclusion

Historical analyses of several centers throughout the USA over a number of decades showed great care for respiratory distress, recognizing that bulbar failure signals insufficiency of respiratory muscles. One approach—already advocated in the 1950s—was to stop neostigmine during respiratory support to prevent the crisis transitioning from an incipient to an objective stage and apnea. Historical review allows us to examine in detail the semiotics of the myasthenia gravis-associated crisis. Breaking down the definitions of these neuro-emergency shows that physicians have embraced subjectivity in the diagnosis and management of myasthenic crisis. We still cannot tell with certainty when to intervene aggressively and which (ostensibly recovered) patients can remain extubated over the long term.

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