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Historical article

Women in the history of neuromuscular medicine

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1. Introduction

Women have been contributing to the field of neuromuscular medicine since the late 19th century. While some commonly used eponyms are named after women, there are other women who are unknown and have gone unrecognized.

We decided to highlight the work of women in neuromuscular medicine from the 19th to mid-20th centuries; this is when women started to join the medical force, but remained underrepresented and had to overcome many obstacles to succeed. Through the mid-20th century, the percentage of female physicians was 5–6% in the United States. By 2017, there were 35.2% active female physicians across all specialties. The 1972 education amendment which prohibited discrimination on the basis of sex was likely partly responsible for this increase [1,2]. Similarly, in the UK, until the mid-1900s the number of women physicians was under 10%, except for a short-lived increase in numbers during the First World War when more women were allowed to enroll in medical school. Laws in the UK also changed in the mid-1900s, and by 2015, 46.13% of physicians in the UK were women [3,4].

We performed an online search of women's contributions to medicine and neurology during the 19th to mid-20th centuries. Women who worked on neuromuscular disorders or basic science relevant to neuromuscular medicine are presented here.

2. Women in the history of neuromuscular medicine

2.1. Augusta Déjerine-Klumpke (1859–1927)

Augusta Déjerine-Klumpke (Fig. 1) was born in San Francisco, USA in 1859, but spent her neurological career in Paris, France. At the age of 12 she moved to Germany and then Switzerland. Following completion of secondary school, her mother moved her family to Paris so that Augusta could pursue a medical career [5,6]. Paris at that time was a center for academic medicine and neurology, where physicians such as Charcot and Duchenne were making many medical advances. In this environment, Augusta began studying science, histology, and anatomy, and spending time on the medical wards. She was so talented that some of her mentors encouraged her to compete for a prestigious and competitive externship. However, this externship was not open to women at that time and, instead, she pursued research at Charité Hospital until she and another woman, Blanche Edwards, were allowed to compete for the position in 1881 [5,6]. Augusta started her externship at the Hotel-Dieu Hospital in 1883. Here she began her work on brachial plexopathies for which she is best known. Erb's palsy, or upper trunk brachial plexopathy, had already been described, but she described the pattern of injury to the nerves in the lower trunk of the brachial plexus and the association of these injuries with Horner's syndrome [7]. She was able to prove experimentally the localization of lesions causing Horner's syndrome; she performed lesions of various nerve roots on dogs, and showed that the syndrome could be recapitulated by proximal lesions to C8/T1 [7].

She obtained her doctoral degree in 1889 and received many awards for her work. She and her husband (Joseph Jules Déjerine) devoted the remainder of their careers to the joint pursuit of research, and she spent this time describing various types of peripheral neuropathies. She and her husband also created an authoritative clinical text, *Anatomie de Centres Nerveux*, to which she is thought to have contributed a large portion of the detailed clinical descriptions and beautiful illustrations [8]. Equally noteworthy, she participated in the rehabilitation of World War I veterans who returned from battle with spinal cord injuries and became a leader in rehabilitation of those with paraplegia.

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Fig. 1. Portrait of Augusta Déjerine-Klumpke and Joseph Jules Déjerine. Credit: Wellcome Collection and CC BY.

2.2. Gabrielle Levy (1886–1935)

Gabrielle Lévy, a French neurologist and neuropathologist, was born in Paris on January 11, 1886 [9]. At first, she was drawn to the arts, especially music [10]. While she maintained this interest, she also developed an interest in medicine. Lévy started her externship in Paris in 1911. She worked at the Pitié-Salpêtrière Hospital, Hôpital Beaujon, and Hôpital des Enfants-Malades between 1912 and 1915 [9]. Subsequently, she started her internship, which she completed in 1918 at the age of 32. From 1918 to 1923, she served as chief of the Salpêtrière laboratory, and was then an assistant professor in the department of pathology from 1923–1926 [10]. While at Salpêtrière, Lévy worked closely with Pierre Marie and his other pupils. She wrote on the neurological consequences of war, as well as published numerous articles on post-encephalitic syndromes. Many of Lévy's articles described post-encephalitic movement disorders, such as parkinsonism, chorea, and myoclonus [9]. Post-encephalitic syndromes became the subject of her 314-page thesis, published in 1922 [10,11].

In 1925, she was appointed as a physician at the Hôpital Paul-Brousse, a neuro-oncology center [10]. While there she worked with Gustav Roussy, another one of Pierre Marie's pupils and the head of the Paul-Brousse Hospital [12]. Together, they described a syndrome characterized by a hereditary polyneuropathy, ataxia, tremor, and foot deformities, first published in 1926. This syndrome is known as the Roussy-Lévy Syndrome or hereditary areflexic dystasia, which was later found to be caused by mutations in the PMP22 gene or the myelin protein zero (MPZ) gene. Roussy and Lévy produced many other papers together, and it is notable that in his obituary for Lévy, Roussy wrote "in our collaboration, in which my name was often mentioned with hers, it was almost always her idea and the largest part was done by her" [13].

Lévy had various other publications; with Lhermitte she published on his eponymous symptom in demyelinating disease [14], she published papers on radiotherapy for brain tumors, and on diabetes insipidus following head injury. In 1934, Lévy died at the age of 48 from a progressive and malignant disease of the nervous system; it is reported that she died from a disease which she was studying, likely from a brain tumor that she diagnosed herself [10].

Fig. 2. Portrait of Lucja Frey.

2.3. Lucja Frey (1889–1942)

Lucja Frey (Fig. 2) was a Jewish neurologist who was born in the Polish city of Lviv (now part of western Ukraine). In 1923, she graduated from medical school at Warsaw University at the age of 34. During her medical training she worked with the chair of the Neurology Clinic (Professor Orzechowski) and after graduation she joined the Department of Neurology at Warsaw University as a senior assistant. In 1929 she returned to Lviv where she worked at the Jewish Community hospital, married, and had two children. In 1941 she and her family were taken to the Lemberg Ghetto where she worked at the clinic. On August 20, 1942 the clinic staff and its patients were killed; it is believed that she was killed at this time [15,16].

Her main contribution to neurology was in 1923 [17]. She published the case of a 25-year-old man who, after a gunshot wound to the left mandible, developed flushing, warmth and sweating in the left side of the face when eating. She described in detail the pathophysiology of this syndrome with both the sympathetic and parasympathetic contributions, and proposed treatment. She did a series of experiments with different agents to support her hypothesis. She concluded that the cause of the symptoms was greatly due to aberrant regeneration of the auriculotemporal nerve. This syndrome is known as auriculo-temporal nerve syndrome, gustatory

Fig. 3. Picture of Mary Broadfoot Walker. Credit: Wellcome Collection and CC BY.

sweating, or Frey syndrome. She published a total of 43 articles during her short career including papers on spinal cord disorders, brain topography, hereditary conditions of the nervous system among others [18,19].

2.4. Mary Broadfoot Walker (1888–1974)

Mary Broadfoot Walker (Fig. 3) was a Scottish neurologist who graduated from an all women's medical school in 1913. She served during World War I and then returned to England to work at St. Alfege's Hospital (a former hospital in South East London). It was during her work at St. Alfege's that she made the discovery that made her famous. She had noticed that the symptoms and signs of myasthenia gravis had some similarities with curare poisoning. She injected physostigmine subcutaneously into a patient with severe myasthenia and demonstrated that it caused temporary improvement of symptoms. The first publication of her findings in 1934 was ignored and met with some skepticism [20]. She then used subcutaneous neostigmine (which was a better tolerated compound) in another patient and demonstrated the dramatic effect of the drug to the Clinical Section of the Royal Society of Medicine [21]. There was still some doubt about her findings as some thought that the patient selected was potentially a "hysteric" [22]. However, shortly after, her findings were rapidly accepted as many started to try neostigmine in their patients with success [22]. Later, an oral formulation of neostigmine became available and she was able to transition the patients to an oral maintenance dose. She received multiple awards for her work in myasthenia gravis. In the field of neuromuscular medicine, she also published the first report of the relationship of hypokalemia with familial periodic paralysis [23–26]. She retired in Scotland and died at the age of 86 [26].

2.5. Gerty Theresa Radnitz Cori (1896–1957)

Gerty Radnitz Cori was a biochemist born in Prague. While in medical school she met her future husband, Carl Cori. She completed her medical studies in 1920, and then worked in Vienna and Prague. However, being a Jewish woman in Europe at that time made it difficult for her to find an academic position [27,28]. She moved with her husband to Buffalo, New York. There was some opposition to them working together and Carl Cori's autobiography mentions that some of the offers he received (which he turned down) required for him to stop working with his wife. As a team, they started working on carbohydrate metabolism and continued their research at Washington University in St. Louis. There, Gerty again encountered discrimination for being a woman; her salary was a tenth of her husband's despite them being equal partners in their laboratory [27,28].

Throughout their career they made multiple discoveries with the most notable one being the description of the cycle known as the Cori cycle. Their work on carbohydrate metabolism [29] and how energy is stored and produced led them to win the Nobel Prize for physiology or medicine in 1947. Gerty Cori was the first American woman and the third woman overall to receive a Nobel Prize in a science category [27,28]. They each also had independent research projects; Gerty's was the identification of the debrancher enzyme which when dysfunctional causes Glycogen Storage disease type III or Cori's disease [30]. This last discovery was made while she battled a 10-year-old illness, myelofibrosis, which was the cause of her death in 1957 [27,28].

2.6. Dorothy Hansine Andersen (1901–1963)

Dorothy Hansine Andersen was an American pediatrician and pathologist. She graduated from Johns Hopkins School of Medicine in 1926 in a class of only six women [31]. She then completed a surgical internship at Strong Memorial Hospital in Rochester, New York, but was later denied a residency spot because she was a woman, as this was against hospital policies at the time. She decided to turn her career toward pediatrics and pathology and joined the department of Pathology at Columbia University in New York City, where she worked for the duration of her career. In 1952 she became chief of pathology and in 1958 she became a full professor [32]. She was known to be exquisitely meticulous with her pathological studies and made two very important contributions to medicine: she was the first to describe cystic fibrosis in 1938 [33] and what is known today as glycogen storage disease type IV in 1956 [34]. She died from lung cancer in 1963.

2.7. Marion Grace Eggleton (1901–1970)

Marion Grace (Palmer) Eggleton was a British physiologist born in 1901. She obtained her Bachelor of Science in physiology in 1923 and medical degree in 1926 at University College, London. She worked at the University of Edinburgh and Bedford College before returning to University College in 1938. Due to war bombings her department was subsequently transferred to Leatherhead, Surrey [35].

In 1927, along with her first husband, Philip Eggleton, she discovered a compound in muscle which they named "phosphagen" because, when hydrolyzed, it yielded inorganic phosphate. This compound rapidly reduced in concentration with muscle contraction [36,37]. They were able to identify "phosphagen" in the skeletal muscles of the frog, tortoise, rabbit and guinea pig. They were also able to demonstrate that the concentration of phosphagen was higher in muscles with more energy output, such as the gastrocnemius. [36,37] This compound was later identified as creatine phosphate. Her other works include descriptions of the effects of crush injury during World War II on renal function, and the effects of alcohol on the Central Nervous System and on diuresis. [38–40]

2.8. Rita Levi-Montalcini (1909–2012)

Rita Levi-Montalcini was born in Turin, Italy in 1909. She overcame many obstacles in her quest to become a physician and a scientist, including her father's opposition to her professional education, Mussolini and his race laws, and initial skepticism of her work regarding Nerve Growth-Stimulating Factor (NGF) [41]. Though her father did not believe in women having a professional career, she pursued medical studies nonetheless. She enrolled in medical school at the University of Turin in 1930. There she met her first mentor, Giuseppe Levi, who exposed her to critical methods that she would use in her later work. She graduated from medical school in 1936 and started training in neurology and psychiatry, which was interrupted by Mussolini's race laws in 1938 banning those of Jewish heritage from academic positions.

Instead of retreating from her medical and scientific career, she continued her experiments privately and set up a makeshift laboratory in her bedroom [42]. She had read Viktor Hamburger's work, and in her lab, repeated his experiments of limb bud removal on neural growth in chick embryos. She extended these findings using histological staining methods she learned in Levi's lab to better visualize neurons, and was able to observe spinal neurons degenerating without stimuli from their environment. She published this work in 1942 and 1943 [43]. In 1942 she fled Turin with her family and moved to the countryside rebuilding her lab there. She did not interrupt her experiments until her family had to flee again when Hitler invaded northern Italy; they went into hiding in Florence, where they waited out the remainder of the war.

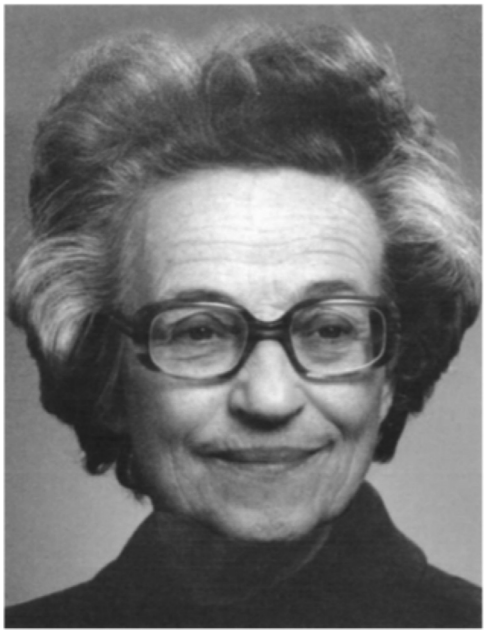

Fig. 4. Picture of Lisa Welander [46].

In 1947 after the war, Viktor Hamburger, who had read her work, invited her to come and work in his lab at Washington University in St. Louis She was able to replicate and expand upon her original findings. She would remain at Washington University for an additional 26 years. There she did exciting experiments investigating how mouse sarcoma tumor could induce neurite outgrowth in chick embryos [44]. In further experiments with Stanley Cohen, they discovered that a substance in snake venom and in mouse salivary glands also had the same properties [45]. They were able to produce an anti-serum that would block the inductive properties of what they would call neuron growth factor (NGF). Stanley Cohen was then able to purify NGF from mouse salivary glands [45]. Together in 1986 they won the Nobel Prize for discoveries of NGF. Rita lived to age 103 and is the longest-lived Nobel Prize winner.

2.9. Lisa Welander (1909–2001)

Lisa Welander (Fig. 4) was a Swedish neurologist born in the town of Frustana. Her parents allowed her to study medicine after she successfully attended an operation without fainting [46]. She graduated from the Karolinska Institute in Stockholm in 1952. She then worked at Umea University where she was Sweden's first professor of Neurology and in 1964 became the head of the Department of Neurology [46].

She had two significant contributions to neurology. One was her doctoral thesis, which she published in 1951. In this thesis [47] she described in great detail the inheritance, clinical manifestations, examination, clinical course, pathology, and electrodiagnostic studies of a disorder she called Myopathia Distalis Tarda Hereditaria (late onset hereditary distal myopathy). She evaluated a total of 249 cases. This was the first time a distal myopathy was described

in such detail and it established the existence of this subtype of myopathy. It is now known that this myopathy is associated with mutations in TIA1 protein and it is more commonly known by the name Welander distal myopathy.

Her second contribution to neurology was the description in collaboration with Erik Kugelberg of the disorder they named Heredofamilial Juvenile Muscular Atrophy, which is now called Kugelberg-Welander syndrome or Spinal Muscular Atrophy type 3. They presented the preliminary results at the Congress of Scandinavian Neurologists in 1952 and then published their findings in 1956 [48]. They described 12 cases with onset of weakness from ages 2–17 (mean 9), progressive atrophy and fasciculations. Pathology and electromyography of these cases showed a neurogenic process [48].

2.10. Judith Graham (1919–1975)

Judith Graham Pool is noteworthy both for her discoveries in the realm of neuromuscular medicine, where she developed valuable techniques for recording from muscles, and in hematology. This work started as a PhD student in Ralph W. Gerard's Lab at the University of Chicago. Here she was able to pull glass micropipettes with tips that were of sufficiently fine diameter ($<5\,\mu m$) to record from frog skeletal muscle [49]. In doing these studies, she was able to both measure a resting membrane potential of $-80\,mV$ from single muscle fibers and to pass current through these micropipettes to stimulate action potentials [50]. These techniques of pulling glass micropipettes have been widely used in electrophysiology labs throughout the world. She also taught physics for a time at Hobart and William Smith College before finishing her dissertation research and publishing this work in 1946 [49].

In addition to these important discoveries in neurobiology, she is even better known for research in hematology, where she developed a technique for purifying clotting factors from blood plasma [51]. This fraction called cryoprecipitate was enriched for Factor VIII, of great need by hemophiliacs. Conveniently, the remaining plasma could be saved for other clinical uses [52]. This technique was widely adopted by blood banks and is still used in various clinical settings to this day.

2.11. Ingrid Gamstorp (1924–2007)

Ingrid Gamstorp, a pediatric neurologist, was born in 1924 in Lund, Sweden. She studied natural sciences in high school, and then enrolled in the University of Lund to study medicine. While in medical school, she cared for people released from Auschwitz and Bergen-Belsen concentration camps [53,54]. In 1956, she defended her doctoral thesis titled "Adynamia Episodica Hereditaria" earning her the Best Dissertation award by the Swedish Medical Association [55]. After defending her thesis, she became an associate professor in pediatrics. In the mid-1960s, she spent a year studying at the Department of Child Neuroscience at Harvard University; when she returned, she was referred to as one of Sweden's best educated child neurologists [53,54]. Upon leaving Lund in 1967, she worked for a period of time as the Head of the Department of Pediatrics of the Central Hospital in Jönköping, Sweden. During this time, she wrote a widely referenced text devoted to neuromuscular disorders in pediatric neurology. In 1972, following her time in Jönköping, she transferred to Uppsala University. She remained at Uppsala University as a professor of child neurology until her retirement in 1989 [54]. She passed away in 2007 at the age of 83. A year before her death, she celebrated her doctoral jubilee (50th anniversary) at Lund University [53].

Professionally, Gamstorp was the first to describe Hyperkalemic Periodic Paralysis, the subject of her thesis [55]. She is also known for her work with Georg Grund and Karl Gunnar Wilhelm Wohlfart in their description of an autosomal dominant syndrome characterized by myotonia and muscle wasting, now known as Gamstorp-Wohlfart Syndrome [56]. She was a skilled diagnostician and received consultations from all over the country. She was also a pioneer in medical ethics [54]. She co-founded the International Child Neurology Association (ICNA) and was involved in the founding of the Nordic Neuropediatric Society [53].

2.12. Ellen Damgaard Andersen

Ellen Damgaard Andersen, a Danish physician, was the first to describe (in collaboration with Peter Krasilnikoff and Hans Overad) the disorder known as Andersen syndrome or Andersen-Tawil syndrome. In 1971, she and her colleagues published a case of an 8-year-old child who had episodes of paralysis, extrasystoles and characteristic developmental abnormalities (low set ears, hypertelorism, mandibular hypoplasia, broad root of nose, clinodactyly) [57].

3. Conclusion

As discussed in this paper, many women made contributions to neuromuscular medicine from the 19th to the mid-20th centuries. These women are examples of perseverance and dedication. They lived remarkable lives that were marked by two world wars. Rather than retreating from academic and medical careers when they met hardship, they overcame gender and religious discrimination to make profound discoveries and improve the lives of many patients. One even tragically died while pursuing these dreams. For many, their initial interest in medicine and discoveries were met with skepticism and their work was not always sufficiently valued and recognized, but over time they went on to win many prestigious awards, including the Nobel Prize. We hope that this review will further highlight their important work leading to broader recognition and celebration of these pioneers in Neuromuscular Medicine.

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