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The Coevolution of the Understanding and Treatment Modalities for Phantom Limb Pain

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ABSTRACT

Phantom Limb Pain (PLP), an inappropriate sensation in a missing limb, is a post-amputation phenomenon that occurs in up to 80% of amputees. The specific sensations vary from person to person, but some common reported sensations include warmth or coldness, itching, tingling, and electric shock. Some patients also perceive a specific position or movement of the phantom limb. Most amputees experience PLP with varying degrees of intensity, frequency, and duration. About 5-10% of amputees continue to have severe PLP for many years after amputation. As technology and scientific understanding have evolved, phantom limb pain has become better understood over the centuries, from its first mention from Ambroise Pare in the 1600s to the usage of a variety of medication, medical therapy, and surgery options available today. Although the field of medicine does not yet have a curative treatment for PLP, treatment modalities have advanced from the use of wooden pegs to the latest and advanced prosthetics. By summarizing the growing understanding and evolution of treatment modalities for the medical condition from its first mention in the 16th century to the current 21st century, we can begin to appreciate the years of study and collaboration to current knowledge of phantom limb pain.

Introduction

Phantom Limb Pain (PLP), an inappropriate sensation in a missing limb, is a post-amputation phenomenon that occurs in up to 80% of amputees. The specific sensations vary from person to person, but some common reported sensations include warmth or coldness, itching, tingling, and electric shock[1]. Some patients also perceive a specific position or movement of the phantom limb. Most amputees experience PLP with varying degrees of intensity, frequency, and duration. About 5-10% of amputees continue to have severe PLP for many years after amputation[2].

The nervous system is integral to body functions. The nervous system is comprised of the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS includes the brain and the spinal cord, while the PNS involves the nerves outside the brain and the spinal cord. The system is functionally split into the sympathetic nervous system and the parasympathetic nervous system. The sympathetic nervous system controls our “fight-or-flight” responses, speeding up our heart rate, while the parasympathetic nervous system slows down our heart rate and lowers blood pressure as our “rest-and-repose” response. Afferent nerve fibers provide sensory input of sensations and efferent nerve fibers send out motor output that innervates target tissues and organs. Using specialized nerve cells called neurons, the nervous system sends signals through a network of nerves. These electrochemical signals are perpetuated through this neuronal network in a manner similar to the way electricity is run through electrical wires. Each neuron propagates this signal using chemical gradients across ion channels. The firing of this signal along an individual neuron is called an action potential. An action potential is initiated at the axon hillock. Potassium ions, K+, leave the neuron and sodium ions, Na+, flow into the neuron. Because there is a larger number of positive ions leaving the cell than entering, an electrochemical gradient occurs, depolarization of the cell[3]. When these nerve fibers are severed or missing due to an amputation, many of these action potentials cannot be propagated and transmitted throughout the body, preventing communication between the brain and specific organs or body parts.

As technology and scientific understanding have evolved, phantom limb pain has become better understood over the centuries. Although the field of medicine does not yet have a curative treatment for PLP, treatment modalities have advanced from the use of wooden pegs to the latest and advanced prosthetics. By summarizing the growing understanding and evolution of treatment modalities for the medical condition from its first mention in the 16th century to the current 21st century, we can begin to appreciate the years of study and collaboration to current knowledge of phantom limb pain.

16th century

16th century Europe saw great advancements in medical knowledge. At the beginning of this period of time, medicine and surgery were considered separate professions. Respected medical professionals were known as spiritual healers, relying on chemical elixirs and ointments. By contrast, anatomy and surgery were more nascent, viewed as less important than medicine, so practical surgical procedures were executed by barber surgeons, who lacked formal academic education. Medical doctrine at this time stated that there were only four fluids, or humors, in the body: blood, phlegm, yellow bile, and black bile. Many diseases were believed to be the result of humoral fluctuations or imbalances. The most common medical practice at the time was bloodletting, the process of withdrawing blood from a person's veins, usually through the use of blood leeches[4]. Bloodletting was employed when doctors believed there was an excess of blood. Neuroscience was not yet a formal area of study. Many Renaissance physicians began to dissect and map out the brain. Belgian anatomist Andreas Vesalius mapped out the nervous system and the relationship between various functions with certain brain regions. He argued that the ventricles acted as the main site of brain functions. Leonardo da Vinci also dissected the brain, sketching the brain from various perspectives[5]. 16th-century anatomists contributed greatly to the physical description of the brain, providing the basis for subsequent theories and treatments later on.

The first documentation of PLP can be traced back to the 16th century. Ambroise Paré, a French barber surgeon, performed amputations with ligatures on patients. Barber surgeons, besides hairdressing and shavings, performed dental extractions, minor surgeries, enemas, and amputations[6]. Paré became familiar with amputations as a battlefield doctor, being one the first to use hot-oil cauterization in limb amputations for hemostasis from bone.

Knowledgeable in designing wooden limbs with movable joints, Paré tried to amputate at places best for artificial legs and arms. Eventually, he started to create more sophisticated artificial limbs with clock springs and metal gears. As Paré's practice went on, he noticed many amputees complained of pain in the missing limb. The patients would experience this pain at rest and long after the wound had healed. Although Paré didn't coin the term phantom limb pain, he was the first to describe the phenomenon. Describing PLP as "strange" and "prodigious," he mentions his patients would complain of "exceeding great pain of the leg so cut off" many months after the procedure. In his 1564 book *Treatise on Surgery*, Pare published his observations, suggesting that PLP originated in the brain, not in the remaining part of the limb[7].

17th century

During the 17th century, physicians questioned traditional medical concepts and practices. With the scientific method, they expanded their knowledge of science and medicine. For example, William Harvey, in 1628, published his theory on the circulation of blood in the body, causing much controversy at the time. Santorio also invented the thermoscope, an early version of a medical thermometer with a visual scale. Regarding medical research, the 17th century consisted mostly of anatomical observations. Anatomist Thomas Willis was the first in trying to link structure of the brain to its function. He removed the brain from the cranium, mapping particular areas of the brain responsible for certain functions, including vision, hearing, and touch. Willis also observed basic reflexes and the arterial supply of the brain[8]. Using his newfound knowledge, he discovered the Circle of Willis, the joining area of several arteries at the inferior side of the brain. Willis's work formed the basis for subsequent theories and treatments for many neurological disorders.

Contemporaneously, Rene Descartes proposed a connection between the brain and other body parts in the aspect of pain. He suggested that pain was a mechanical sensation communicated to the brain, where the message from the injured body area is relayed to the brain and recognized as pain. To stop the brain's recognition of pain, one would have to repair the injured body part or prevent the message from reaching the brain through the use of analgesic drugs[9].

18th century

Often referred to as the Age of Enlightenment, the 1700s included many new publications on a better understanding of body structure and function on a more minute and detailed level. Antoni van Leeuwenhoek cut through the optic nerve of a bull and, by the use of the microscope, described the cross section of a nerve fiber, surrounded by fat and connective tissue[10]. It was also during this time when the idea of only four humors was corrected. Emanuel Swedenborg, a mining engineer, discovered cerebral spinal fluid, CSF, in the ventricles of the brain, the medulla oblongata, and spinal cord[11]. Regarding the experience of pain, physicians and researchers began to adopt a more nuanced view, whereby both physiology and psychology of the individual influenced the overall pain experience. To this end, Albrecht von Haller was the first to discover that only nerves produced sensations and the nervous system is the vehicle by which these sensations were communicated and experienced. It was during the 18th century when a trend started to develop, where research focused mainly on specific characteristics of pain. Pierre Jean George Cabanis incorporated the emotional component to pain research. He believed that pain promoted stability, balance, and equilibrium to the nervous system. His theory eventually led to the therapeutic techniques of electrical shock and stimulation. Cabanis not only proposed that pain could be useful, he also suggested that pain sensations are not just a pure physiological reaction to a stimulus, but it also requires mental activity of the subject, sparking the idea that pain experience is modulated by both physical stimulus, as well as mental activity. He thus founded the notion of psychogenic pain[12]. These findings of the 18th century provide the foundational framework for phantom limb pain, specifically the concept of psychophysiological pain.

19th century

In the 1800s, the Industrial Revolution resulted in much scientific and technological development, which led to new experiments and discoveries. In 1813, Felix Vicq d'Azyr discovered the claustrum, which occupies about 0.25% of the human cerebral cortex and is the thin sheet of neurons that is commonly referred to as the "wall of the brain"[13]. During the mid-1800s, Phineas Gage, an American construction foreman, was involved in a railroad construction accident. While packing explosive powder into a hole, the powder detonated, launching a tamping iron into Gage's left cheek and through his brain, eventually exiting through his skull and landing several dozen feet away. Although Gage became blind in his left eye, he survived and was even able to communicate clearly to a doctor later that day. One major observation, which makes this case iconic, was the change to his behavior and personality. Being originally known as a polite and mild-mannered man, he subsequently would commonly use profanity and behave inappropriately in social situations. His friends described him as "no longer Gage". This drastic change in character was ascribed to the damage done to his frontal lobe[14].

Later in the 19th century, the American Civil War occurred, accompanied by many serious injuries, some of which resulted in amputations. Sila Weir Mitchell, an U.S. Civil War surgeon, officially coined the term 'phantom limb pain', describing the phenomenon as vivid and strange hallucinations due to the vivid descriptions patients had after amputation[15]. One amputee who lost her arm due to cancer recounted feeling like she was "wearing an elbow length evening glove" and "everywhere the glove touches [her] skin it's crushing [her] arm constantly." Many of his amputee patients also reported sensations of severe burning pain and muscle clenching in the missing limb, which Mitchell described as phantom pain[16]. During this time, many clinicians categorized PLP as a psychological problem, due to the limited knowledge of the disorder; however, as time progressed and technology advanced, scientists and medical professionals finally began to correctly recognize these sensations.

20th century

Within the 20th century, World War II saw a lot of injuries and amputations. Nearly 15,000 U.S. service members lost a limb during combat. Common procedures used by army surgeons included the drainage of osteomyelitis, sequestrectomy (the removal of residual limb tissue and bone), and the closing off the residual limb. Major General Norman T. Kirk was responsible for about 600,000 wounded soldiers, many of whom were amputees. He studied 1700 of these amputees, operating on more than 700 of them. Learning from his experiences in the war, he helped returning service men with wound closure, stump healing, and initial prosthetic fitting. Though physical therapy was fairly nascent during this time, Kirk developed progressive, standardized protocols for wound care and daily activities. He was a proponent of open circular amputation, which allowed for better prosthetic fitting and improved limb function for the patient. Kirk also developed clinical policies for initial prosthetic fitting during his time at the army general hospital, many of which are still applied today[17].

Many amputees suffered with sensations relating to phantom limb pain, but chose to not publicly share their experiences out of fear of being labeled and outcast as mentally ill. In the early 20th century, many theories assumed that PLP was manifested by hysteria and denial, caused by neurosis. R.D. Langdale Kelham, a researcher in post-amputation rehabilitation, described that a typical PLP patient most often had an "unsatisfactory personality". However, theories relying on psychopathology were quickly debunked. By the end of the 1900s, a more popular theory was recognized and established regarding the cause of PLP, namely that the anatomical origins of PLP were in the sensorimotor area of the brain. In the human brain, the primary somatosensory cortex, located in the anterior part of the parietal lobe, consists of areas corresponding to specific parts of the human body. The mapping of the cortical homunculus, a proportionate representation of afferent innervation, allows for visualization of different limbs in the somatosensory cortex. It has been theorized that maladaptive brain plasticity occurs in many PLP patients. Based on an observation in monkeys with arm deafferentation, loss of input to the brain region responsible for hand sensation led to editing of the somatosensory map, otherwise known as brain plasticity. This brain plasticity can be harmful as it can trigger pain in the phantom hand as a result of mismatched sensory inputs. Surgical interventions were used to fix maladaptive plasticity, but these had poor clinical outcomes. Medical professionals then turned to treatments focused on reversing maladaptive reorganization (trying to re-edit the cortical map). A popular treatment used to reinstate the representation of the missing limb to its original territory in the somatosensory cortex is mirror box therapy[16]. Neuroscientist Vilayanur S. Ramachandran used a mirror, placed vertically in the middle of a wooden box, to mirror the healthy hand of a patient with an amputated hand. Moving the healthy hand supposedly restored the missing hand representation in the primary sensory cortex, resurrecting the phantom limb. Through Ramachandran's mirror box therapy, many patients reported drastic improvement in their conditions[18]. Like mirror therapy, as technological advancements were made, virtual therapy became a new technique aimed to improve phantom pain.

21st century

Moving into modern times, the research, and theories about phantom limb pain, as well as useful therapy treatments, continue to be used and applied in patients today. As of now, approximately 185,000 amputations occur in the United

States, according to the Amputee Coalition[19]. With the variety of medications, medical therapy, and surgery options, amputated patients diagnosed with PLP are able to rely on these treatments to relieve phantom pain. Some medications include over-the-counter pain relievers, antidepressants, and narcotics. Mirror box therapy, spinal cord stimulation, as well as deep brain stimulation surgery are also used to alleviate phantom pain[20]. Along with these new treatments and techniques for PLP, prosthesis have been continuously evolving since the original wooden and leather artificial limbs. Current models are now made of carbon fiber and thermoplastics, lightening the weight and strengthening the prosthetic limb. Some are even electric and have microprocessor implantations that allow for better joint movement and limb function. The most advanced prosthesis is able to connect the artificial limb with the human nerve system, a mind-controlled limb[21]. A prosthetic arm that uses artificial nerves that grant the patient a near-natural sense of touch is currently being tested and experimented on. Researchers at Stanford University have developed an artificial sensory nerve that is able to pick up on pressure cues, sending electrical pulses in patterns like those produced by biological neurons[22].

The 2000s also saw an increased use of MRIs, magnetic resonance imaging, as a noninvasive way to examine various organs and structures in the body. Using a large magnet and radio waves, MRI scans are frequently used to provide an image of the brain and spinal cord without having to perform surgery. Under the umbrella of MRIs, fMRI (function MRI) is a special type of magnetic resonance imaging where brain activity is measured through blood flow changes[23]. With technology used in MRIs, detection and diagnosis of tumors, certain diseases, inflammation, infection, and vascular irregularities are faster and easier. Unlike CT scans and X-rays, MRIs do not require radiation exposure, making it safer for people vulnerable to the effects of radiation, like pregnant women and babies[24]. Although we know the neural basis of PLP and have many treatments and therapies available, we still don't have an extensive, profound understanding of the disorder just yet; however, with enough persistence and dedication to the insight and research, our understanding and treatment modalities for PLP can be evolved and improved to be of better service to patient with phantom limb pain.

Conclusion

The awareness, understanding, and treatment landscape for amputations and PLP has advanced very far from its first mention from Ambroise Pare in the 1600s. The coevolution of technology and understanding, especially over the last century or so, has provided a solid foundation upon which new biomedical innovations have advanced therapies for PLP. Despite this progress, we still do not have a comprehensive understanding of the inner mechanisms of PLP. Continued research and effort in both theory and technology are key to improving understanding in the future, and ultimately better serve the patients who suffer from PLP.

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