Clinical and historical aspects of the Elephant Man: Exploring the facts and the myths

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ABSTRACT

Joseph Merrick, the Elephant Man, presented to the Royal London Hospital in 1884 with an obscure condition that puzzled his contemporaries, and fascinates clinicians to this day. Throughout the 1900s, a number of theories were advanced to explain the numerous growths that covered his body: neurofibromatosis, Proteus syndrome, and a combination of childhood injury, fibrous dysplasia, and pyarthrosis. The debate continued throughout the 20th century without resolution. Today, new consensus on the genetic and clinical diagnosis of neurofibromatosis and Proteus syndrome has allowed advancements in the Elephant Man’s diagnosis. Using recent clinical diagnostic criteria it is now possible to conclude that Joseph Merrick was in all likelihood suffering from Proteus syndrome. Nevertheless, details of his genotype remain unknown. Obtaining intact DNA from the Elephant Man’s skeleton is challenging, yet it is possible that sequencing Merrick’s genome could provide genetic confirmation of his clinical diagnosis, and shed light on the process of tumourigenesis.

The Elephant Man is a character with whom many of us are familiar. He was first brought to popular attention in 1971, when Ashley Montagu, a distinguished anthropologist, published the story of his life. Entitled The Elephant Man: A Study in Human Dignity, Montagu’s work explored the effects of environment and circumstance on the development of a person’s character (Montagu, 1971). This theme was further explored in David Lynch’s Oscar-nominated film, The Elephant Man, which chronicled the life of its eponymous hero, and presented him as a man of great kindness and his ability to rise above the hardships of his daily life, which enthralled us most.

Joseph Merrick first presented to the Royal London Hospital in 1884 at the age of 21. He was brought for examination by Sir Frederick Treves, Surgeon Extraordinary to Queen Victoria, who had met Merrick in a vacant greengrocer’s opposite the hospital where he worked (Treves, 1923). Merrick’s primary complaint was the large number of unexplained growths that began appearing across his body as a child that had been growing in size and number. These growths distorted and disabled his body, making it difficult for him to speak, sleep, walk, and even appear in public (Treves, 1923).

On examination, Treves found Merrick’s symptoms to be primarily dermatological and musculoskeletal in origin (Treves, 1885). Merrick’s dermatological deformities were of two types: an increased quantity of subcutaneous tissue, leading to the development of large pendulous folds of skin hanging from his right pectoral region, axilla, and buttocks; and a papillomatous epidermis, extending across the aforementioned lesions and other areas of the body (Treves, 1885). These papillomatous lesions were large and covered the majority of his body, with deep sulci, discoloration, and a foul odour (Treves, 1885).

Merrick’s musculoskeletal deformities consisted of an injury to the left hip (requiring him to walk with a cane), scoliosis of the spine, and deformities of his right arm, both legs, and skull (Treves, 1885). While Merrick’s hip disease was attributable to a childhood injury, his scoliosis and limb deformities were due to localized hypertrophy of the skin and bone (Treves, 1885). His right arm and hand were greatly increased in size, with hypertrophy of the bones, misshapen fingers, and overgrowth of skin (Treves, 1885). There was loss of movement and coordination below the elbow on this side of Merrick’s body, although the left was normal. Both of his feet were misshapen with enlarged bones and hypertrophy of the plantar surface (Treves, 1885).

Furthermore, Merrick’s skull was grossly enlarged, asymmetrical, and covered with substantial exostoses protruding from the frontal, parietal, and occipital bones (Treves, 1885). However, he had no cranial nerve paralysis and never suffered from headaches or neurological disturbance (Treves, 1885).
Treves did not come across Merrick by chance. He heard reports of a man with the characteristics of an elephant exhibiting himself in the ‘Freak Show’ that had taken up residence in the empty row of shops opposite where he worked (Treves, 1923). Intrigued, he paid a shilling to the show’s proprietor to be allowed a private viewing while the exhibition was closed (Treves, 1923). It was this meeting that eventually transformed Joseph Merrick from a Victorian freak show exhibition to the Elephant Man—a great personality, medical mystery, and popular culture icon.

Treves’ first meeting with Merrick was not portentous of the great friendship that would grow between these men in their later years. He described Merrick as “the most disgusting specimen of humanity that I have ever seen” (p3) and went on to perform a detailed examination, during which he “made little of the man himself” (p7) (Treves, 1923). At that point, it is clear that Treves viewed Merrick as little more than a medical curiosity. He examined him, published a report, and did little to diagnose or help Merrick. However, he gave him his card, which is how Merrick became entrusted to Treves’ care two years later.

By this time, much had changed in Victorian Britain: the freak shows, which had once lined the streets, were now illegal. Following a trip abroad during which he was robbed of his life savings by his show manager, Merrick found himself stranded at Liverpool Street Station with no money, nowhere to go, and unable to make himself understood due to his speech impediment (Treves, 1923). The police picked him up, found Treves’ card in his pocket, and dropped Merrick off at the Royal London Hospital (Treves, 1923).

Treves admitted Merrick to the hospital, but was forced to apply for special dispensation from the chairman of the committee to house a chronic case (Treves, 1923). Mr. Carr Gomm, chairman of the committee, wrote a letter to the Times asking for financial support from the public, and within a week, sufficient money was raised to feed and house Merrick on the hospital grounds for the remainder of his life (Treves, 1923). Treves and Merrick became great friends and spent many afternoons together until Merrick died peacefully in his sleep in 1890 (Treves, 1923).

At Merrick's death, his disorder remained undiagnosed. Treves and his colleagues had focused more on the description of Merrick's ailments than their diagnosis. Merrick himself had an explanation for his ailment that centred on the idea of maternal impression—a well-accepted medical theory at the time (Durbach, 2007). According to Merrick, his mother had received a great fright while pregnant with him when she was knocked down by an elephant at a fairground (Treves, 1885). This experience had been ‘imprinted’ on him while just a foetus, leading to the development of his elephantine characteristics. Several contemporaneous cases of maternal impression had been published, such as that reported by Lewis Jones, MD in the BMJ in 1895, wherein a pregnant mother is described as being “startled by a little boy who has two fingers of one hand fused together” (Jones, 1895).

At birth, her child had a double fifth toe on each foot, and Jones finds himself convinced, noting “the relation between the alleged cause and effect [is] a fairly direct one” (Jones, 1895).

The concept of maternal impression eventually lost favour within the medical field, and in 1909, dermatologist Parkes Weber proposed that Merrick’s presentation could be explained by a case of von Recklinghausen’s disease (Parkes, 1909), or neurofibromatosis type 1 (NF1) as it is known today. NF1 is a relatively common (occurring in 1 in every 3000) autosomal dominant mutation of the neurofibromin gene on chromosome 17, which leads to the development of small nerve and connective tissue tumours (neurofibromata) throughout the body (Brosius, 2010). Diagnosis can be made via genetic sequencing or clinically, using the USA National Institute of Health’s Neurofibromatosis 1 Classical Diagnostic Criteria (Tadini et al., 2014). In order for a diagnosis of NF1 to be considered, an individual must present with at least two of the following: two or more neurofibromas, six or more café-au-lait macules (with a diameter >5 mm pre-puberty and >15 mm post-puberty), freckling in the inguinal region or axilla, two or more iris hamartomas, optic glioma, a distinctive osseous lesion, or a certain aspect of Merrick’s physicality do not correspond directly with NF1 as determined by the above criteria (Anon., 1988).

A diagnosis of NF1 would indeed explain the soft tissue tumours apparent across Merrick’s body, along with the lack of mobility and dexterity in his right arm, which may have been caused by the growths impinging upon his brachial plexus. A diagnosis of neurofibromatosis may even explain the large folds of skin on his right axilla and lower back, which could be pleomorphic neurofibromas (Brosius, 2010). Indeed, a study of radiographs taken from Merrick’s bones in 1982 confirmed that some areas of Merrick’s bones did show the sequelae of pleomorphic neurofibromas (Bean et al., 1982).

Despite the similarities between Merrick’s condition and neurofibromatosis, certain aspects of Merrick’s physicality do not correspond directly with this diagnosis. Firstly, the severity of symptoms experienced by Merrick is unlike any other case to have been described since (Ablon, 1995). Secondly, despite being examined in detail both by Treves and Harvey Crocker, a contemporary dermatologist (Crocker, 1905), Merrick was not reported to have two of the seminal features of NF1: café-au-lait spots or axillary freckling (Brosius, 2010). Both of these characteristics are present in 99% of patients with NF1 and their omission seems significant (Brosius, 2010). Thirdly, Merrick’s family history was negative for NF1 (Tibbles and Cohen, 1986). As a genetic disorder, one might expect to see other cases of NF1 in Merrick’s family history to support his diagnosis. However, NF1 does have a surprisingly high sporadic mutation rate, with approximately 50% of cases being caused by a novel mutation (Légendre et al., 2011). The lack of family history is not therefore a complete contraindication to the neurofibromatosis theory. Finally, in the same study of radiographs in which Bean et al. purported to discover signs of neurofibromatosis in Merrick’s bones, they also found signs that could not be explained by the condition (Bean et al., 1982). In fact, they proposed that a combination of diseases provided the best explanation for Merrick’s condition: neurofibromatosis, fibrous dysplasia and pyarthrosis (the authors also toyed with the idea of Paget’s disease but were “reluctant to inject an additional osseous entity to the three we already have” (p159) (Bean et al., 1982)).

The diagnosis of neurofibromatosis in Joseph Merrick was therefore inconclusive until in 1986, two Canadian researchers, Tibbles and Cohen, revived the discussion of the Elephant Man by postulating a new diagnosis: Proteus syndrome, a hamartomatous syndrome of variable clinical manifestation (Tibbles and Cohen, 1986). It was first described by Cohen and Hayden in 1979 (Alves et al., 2012), and named after the Greek god Proteus (‘the polymorphous’) by Wiedemann in 1983 (Wiedemann et al., 1983). Due to its rarity, with an estimated incidence of fewer than 1 in 1,000,000 (Légendre et al., 2011), its diagnostic criteria has been slow to develop. The most recently devised diagnostic criteria were compiled by Biesecker (2006) (revised from a previous paper by the same author in 1999 (Biesecker, 2006)). It includes a list of three mandatory general criteria (mosaic distribution of lesions, sporadic occurrence, and progressive course) alongside a list of various specific criteria which vary significantly between cases, yet include cerebrofornal connective tissue naevoid (‘skin lesions characterized by deep grooves and gyrations as seen on the surface of the brain’), asymmetric, disproportionate overgrowth, and dysregulated adipose tissue (Biesecker, 2006).

For several years, the diagnosis of Proteus in Merrick remained problematic due to the variability and uncertainty surrounding the syndrome itself. There was considerable confusion surrounding the diagnostic criteria (which is perhaps unsurprising considering fewer than 205 cases have been described in recent years) and the aetiology of the disease (Légendre et al., 2011). Proteus was thought to be due to a somatic mutation that was lethal when occurring in the germ line, which would explain the mosaic distribution of its effects (Lindhurst et al., 2011). However, the mutation that was responsible for these effects remained unknown.
In the early 2000s, several studies (Zhou et al., 2001; Smith et al., 2002) reported an association between Proteus syndrome and mutations in PTEN, a gene involved in cell cycle regulation. However, the results of these studies were controversial due to their small size and the irreducible use of diagnostic criteria in selecting Proteus patients for analysis (Biesecker, 2006). In fact, it was later found that mutation of the PTEN gene is responsible for a different syndrome with similar manifestations to Proteus, known as SOLAMEN (segmental overgrowth, lipomatosis, arteriovenous malformation and epidermal naevoid) (De Souza, 2012). The irregular use of diagnostic criteria in these studies may be responsible for the association of PTEN with Proteus, when in fact the participants were suffering from SOLAMEN.

In 2011, Lindhurst et al. completed a study on 29 patients with Proteus syndrome and found that 26 out of 29 of them had a somatic activating mutation (c.49G>A, p.Glu17Lys) in the AKT1 gene (Lindhurst et al., 2011). Importantly, this mutation was found more commonly in tissue samples from affected areas of the body, than in unaffected areas, confirming the suspicion of mosaicism in Proteus patients (Lindhurst et al., 2011). No other known genomic abnormalities were identified in the three patients not showing AKT1 mutations (Lindhurst et al., 2011). It is possible that the failure to identify AKT1 mutations in these patients is a result of chance, as only a small number of samples (2–3) were taken from each individual (Lindhurst et al., 2011). Due to its mosaic presentation, the mutation leading to Proteus cannot be present in every cell of the body, meaning that it may not be present in all samples. It is also possible that mutations of the AKT1 gene other than c.49G>A, p.Glu17Lys are responsible for the Proteus phenotype in these individuals (Lindhurst et al., 2011). However, complete sequencing of the AKT1 exons and adjacent introns showed no known abnormalities (Lindhurst et al., 2011).

Proteus syndrome is now understood to be the result of an AKT1 mutation. The identification of a genetic basis for Proteus, alongside the development of consistent international diagnostic criteria has overcome much of the uncertainty surrounding the syndrome. Application of Biesecker’s (2006) diagnostic criteria to Merrick, using data from both Treves’ examination and Merrick’s skeleton, shows the he was likely suffering from Proteus. The three mandatory criteria for the diagnosis of Proteus Syndrome are a sporadic occurrence, mosaic pattern of lesions, and progressive course (Biesecker, 2006). Merrick demonstrated all three of these characteristics: the syndrome that affected him was sporadic, with no previous family history, and the growths that covered his body were distributed in a mosaic pattern with a progressive course.

The diagnostic criteria also include a list of various specific criteria also evident in Merrick: cerebriform connective tissue naevi (these resemble almost exactly Treves’s description of the papillomatous lesions across Merrick’s skin) and hyperostosis of the skull. Together, the diagnostic criteria of Proteus explains both the occurrence of the above features in Merrick, and the presence of those features not explained by the previous NF1 diagnosis: macrocephaly, hypothrophy of long bones, and plantar hyperplasia (Tibbles and Cohen, 1986).

With the advent of modern genetics, many have sought to confirm Merrick’s diagnosis through the sequencing of his genome, or any fragments of his DNA that can be acquired. Unfortunately, while Merrick’s bones are preserved in the pathology museum of the Royal London Hospital, they were mostly bleached and boiled in accordance with Victorian preservation techniques. This has lead to substantial degradation of any remaining DNA.

Histological samples of Merrick’s skin were taken by Treves and his contemporaries upon Merrick’s death; however, these too have been destroyed, albeit via a different mechanism. The pathology lab in which they were stored was hit by a bomb during the Second World War, after which the samples became desiccated and were disposed of (Seward, 1986).

Obtaining full and detailed sequences of Merrick’s DNA thus seems improbable. Nevertheless, there is hope that this might one day be achieved. Not only would obtaining a full genomic sequence help solve a fascinating medical mystery, it might also shed light on the genetic pathways involved in the development of cancer.

Merrick suffered from a tumourigenic disorder, one in which uncontrolled growth occurred in many of the cells of his body. While Merrick’s tumours were benign, a similar aetiology could underlie the uncontrolled growth of his tumours and those of a malignant nature. Indeed, all of the genes that have been implicated in Merrick’s differential diagnosis are in some way implicated in cell cycle regulation: neurofibromin is a tumour suppressor gene, PTEN is a tumour suppressor gene and AKT1 is an oncogene (Brosius, 2010; Smith et al., 2002; Lindhurst et al., 2011). Furthermore, the c.49G>A, p.Glu17Lys AKT1 variant associated with Proteus syndrome has already been identified in some samples of cancers of the breast, lung, thyroid, endometrium, and urinary tract (Lindhurst et al., 2011).

Today, 123 years after Merrick’s death, it is hoped that historical medical genetics may finalize the diagnosis of a well-loved character and shed light on tumourigenesis in cancer. We must now contend with our historical preservation methods as we seek to assemble complete genetic sequences from Joseph Merrick, the Elephant Man.

References


