**Misdiagnosis due to Physical Characteristics**

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Although scientists and doctors stand apart by their capability of diagnosis and their overabundance of knowledge, use of technological developments is vital to an individual in the medical-field, as it additionally clarifies to reduce error in the genetic testing and diagnosis. A 24-year-old Japanese woman was cross-examined in her later years, to find that she was misdiagnosed at birth due to phenotypic generalities of her syndrome. Although she was originally diagnosed with CHARGE syndrome, a genetic screening in her 23rd year apprehended her true diagnosis of Kabuki syndrome. Although the physical abnormalities of the mutual conditions are analogous, the genetic mutation resides within different chromosomes in the human body. Misdiagnosis due to physical characteristics is evident in not only this medical case but multiple others. The improvement of genetic testing and technological advancements should not encourage but oppose complacency of doctors and scientists. Specifically, this article proposes and requires the importance in balance of technology and brain power in contemporary society.

**Introduction**

Often, doctors and scientists elect physical characteristics of a syndrome or condition with comprehended knowledge and label a diagnosis without probing deeper into the genetic makeup of a patient. In the National Scientific Journal “Frontiers in Genetics”, a woman anticipated a diagnosis of CHARGE syndrome, an acronym for Coloboma, Heart disease, Atresia Choanae, Retarded growth and development, Genital hypoplasia, and Ear anomalies and/or deafness, due to physical abnormalities until a genetic screening was completed to find that the chromosome responsible for the syndrome was standard and the diagnosis was unfitting. After 23 years, the woman was approached after an appointment with a physician, and was then genetically screened for malformations in her chromosomes. It was only then that the Doctor’s concluded that it was not possible for her to have CHARGE syndrome, as the chromosome associated with the CHARGE mutation was completely functional, and diagnosed her with Kabuki Syndrome after discovering the transfigured chromosome. Although there were no health repercussions for this misdiagnosis because of the drastic similarity of the two, there have been multiple cases in which the patient had detrimental effects because of misdiagnosis.

**Recent Progress**

The patient, at the time of her birth, was “presented with multiple dysmorphic features including choanal atresia, cleft palate, micrognathia, a hypoplastic cupped auricle with atresia of the external auditory meatus, and right facial nerve palsy”, as well as “deafness and bilateral hypoplastic nipples” (Sakata, et. Al), although, there were no heart abnormalities when an echocardiograph was taken. Additionally, “no coloboma was observed in either eye, together with no abnormalities in the iris, retina, choroid, or optic disk” (Sakata, et. Al). Her chromosomal analysis revealed a normal karyotype (46, XX). The fundamental characteristics identifying CHARGE syndrome were transcribed in two scientific papers, the original system written by K.D. Blake and team as well as an updated version in 2005 written and edited by A. Verloes. According to the write-up composed by Blake and his colleagues, the patient met the diagnostic criteria within:

“three major criteria: choanal atresia, characteristic ear abnormalities and cranial nerve dysfunction, and four minor criteria: developmental delay, growth deficiency, an orofacial cleft and genital hypoplasia (based on the finding of hypogonadotropic hypogonadism). She met the diagnostic criteria of typical CHARGE syndrome defined by Verloes by fulfilling two major signs: choanal atresia and hypoplastic semi-circular canals, and four minor signs: rhombencephalic dysfunction, hypothalamo-hypophyseal dysfunction, abnormalities of the middle and external ear, and mental retardation” (Sakata, et. Al).

Furthermore, the patient faced testing as there were complications with hypothyroidism and low serum levels of insulin-like growth factor; The patient’s growth hormone was completely deficient. Moreover, an oral glucose test revealed that the patient held “borderline diabetes with impaired insulin secretion” (Sakata, et. Al). To assist the health concerns, “the patient started treatment with levothyroxine, alfacalcidol, and GH. Her growth velocity dramatically improved after starting growth hormone therapy” (Sakata, et al). Seven months after GH (growth hormone) Therapy began, “the repeated oral glucose tolerance test showed borderline diabetes with impaired insulin secretion … without insulin resistance”. Furthermore, insulin therapy was necessary after 3 years’ time, due to a developed and evolved diabetes mellitus. Against medical generalities, the patient “did not show choanal atresia or heart defects which are frequently identified in patients with CHARGE syndrome” (Sakata, et. Al). Choanal atresia is the blockage of the nasal passage by abnormal bony or soft tissue; this is a result of malformation or lack thereof during fetal development, and the patient did not have either of these indications. The patient suffered multiple surgeries due to her diagnosis, for example treatment of an epicanthal fold of her left eye as well as choanal atresia at one year old. Nevertheless, the patient fit phenotypically into these characteristics of the CHARGE syndrome, and she was given her diagnosis.

Nevertheless, twenty-two years later, the patient completed a Trusight One sequencing panel to reveal her life-altering genetic constitution. A “comprehensive genetic analysis identified a de novo germline mutation, L3564V, in KMT2D” (Sakata, et. Al). This mutation was due to an abnormal transfiguration, being the initial mutation in a family history, identified as *de novo*. Although “archetypal [physical] symptoms of CHARGE syndrome [were present]” (Sakata, et. Al). *CHD7*, the mutation responsible for CHARGE syndrome was customary, in contrast, variance was found on KMT2D, thus the patient was diagnosed with KS after the testing. KS, standing for Kabuki Syndrome, is named after the comparison of diagnosed patients with traditional Japanese makeup in a Kabuki theatre. Kabuki Syndrome physiognomies are often defined by high-arched eyebrows, long eyelashes, everted lower eyelids, a flat, broad tip of the nose, and large protruding ear lobes. Additionally, persons diagnosed with Kabuki syndrome have mild to severe “developmental and intellectual disability, microcephaly, and hypotonia, as well as issues with muscles holding eye movement and rapid, involuntary movement”. Correspondingly, “bilateral atresia of the external auditory meatus, hypoplasia of the right vestibular aqueduct, bilateral hypoplasia of the long limb of incus, and bilateral agenesis of stapes and the posterior semicircular canal [are also disclosed as characteristics of KS]”.

In hindsight, CHARGE and KS are similar in somatic manifestation, and the inadequate confusion of treatments that would cause potential harm in the patient are slight. There have been confusions between CHARGE and KS in previous findings; “[Ming et al., 2003](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5732153/#B22); [Genevieve et al., 2004](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5732153/#B9); [Schulz et al., 2014](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5732153/#B33); [Verhagen et al., 2014](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5732153/#B35); [Badalato et al., 2017](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5732153/#B2); [Butcher et al., 2017](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5732153/#B7)” (Sakata, et. Al) whom all studied and described the correspondence of physical abnormalities between CHARGE syndrome and KS. As a standard, coloboma, a hereditary disfigurement of the eye affecting the lens, iris, or retina, affects patients with CHARGE syndrome as well as diagnosed with KS.

**Discussion**

In this circumstance, the two syndromes were interrelated in a sense of physical manifestation and approached similarly, allowing little to no room for conflict between identification and management; in other occurrences, this would not be the case. The potential of fatality increases as the awareness of assumptions in diagnosis of genetic mutations rises. Multiple instances of malpractice and miscommunication of disorders are being discovered yet further research is still required; knowledge of this is necessary to prevent misdiagnosis in the future. KS and CHARGE syndrome are nowhere near the only syndromes that have been confused because of a lack of testing; for example, a case was reported in 2016 of a fatal misdiagnosis. Long-QT syndrome, what the male adolescent was diagnosed with, was a mutation that was prevalent in his family, he was diagnosed with this syndrome under assumption, and the results ended up being fatal as he was tested post-mortem to show he had an unknown, different syndrome and it was likely the medications he was taking that induced death (Ackerman 2016). There are numerous cases online of misdiagnosis and malpractice on patients, these are just two examples.

Moving forward, genetic disorders and conditions should be extensively discussed to find the inaccuracy among patients. Although there were no significant damages in the CHARGE and KS case, the imprecision because of physical characteristics versus genetic testing could cause a potential impending impairment. A thorough, technical, genetic screening should be mandatory prior to diagnosis by scientist or physician, despite the features associated with an evident syndrome, due to the ability of misdiagnosis leading to mortality.

CHARGE and KS, examined through the research, allows for slight error due to the many overlapping characteristics, although this is not the case for many syndromes. Furthermore, the genetic sequencing of each syndrome is variably separate. This emphasizes the impact and further influence of thorough genetic analysis and sequencing for diagnosis of rare genetic disorders with nonconforming indicators.

**References**

Ackerman. "Abstract 19858: The Promise and Peril of the Molecular Autopsy: Genetic Testing in a Sibling of a Sudden Death in the Young Victim Leads to Misdiagnosis of Long QT Syndrome and ICD Implantation." *Circulation : Journal of the American Heart Association.*134 (2016): Web.

Sakata, Sonoko, et al. “Individual Clinically Diagnosed with CHARGE Syndrome but with a Mutation in KMT2D, a Gene Associated with Kabuki Syndrome: A Case Report.” Frontiers in Genetics, vol. 8, Nov. 2017.