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The 11p15.5 chromosomal region: When did the instability occur?

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ABSTRACT

The disturbances of the 11p15.5 chromosomal region are associated with Beckwith-Wiedemann syndrome, Russell-Silver syndrome, Wilms tumor, IMAGe syndrome, and idiopathic hemihyperplasia. The aim of this research was to examine the hypothesis that 11p15.5 initially became unstable in the European population about 200 years ago. The medical literature from 1557 onwards, especially treatises on teratology, body asymmetry, and books of normal and pathologic anatomy, was searched for any mentioning of lateral body asymmetry, macroglossia and other possible visually detectable symptoms associated with the above-mentioned syndromes. The results indicate that lateral body asymmetry was not described before the first half of the 19th century, it was mentioned in the 1820s, and the first description of a true case was published in 1850. All first cases of hemihyperplasia were reported in continental Europe. Historical data suggest that the 11p15.5 chromosomal region became unstable in the first half of the 19th century. Our preliminary hypothesis is that de novo mutation occurred in continental Europe. Additional genetic research is needed to investigate the development of 11p15.5 instability during this period.

Introduction

IMAGe syndrome was described in 1999 [1]. Beckwith-Wiedemann syndrome was described in the 1960s [2]. Russell-Silver syndrome was described in the 1950s [3]. Wilms tumor was described in 1872 as nephroblastoma and became known as Wilms tumor after 1899 [4]. Idiopathic hemihyperplasia (IH) (congenital hemihypertrophy, hemigigantism, lateralized overgrowth) was described sometime in the first half of the 19th century that will be analyzed below. All these disorders are associated with disturbances of the 11p15.5 chromosomal region [5]. Lateral body asymmetry (LBA) can present itself either as hemihyperplasia (IH and Beckwith-Wiedemann syndrome) or as hemihypoplasia (IMAGe syndrome and Russell-Silver syndrome). It does not require surgical intervention, biopsy, X-Rays, MRI, molecular analysis, and genetic counseling for diagnosis. The diagnosis is made by observation of a patient (Fig. 1). The question arises why LBA was overlooked for centuries of development of medical science? Three centuries is a period extremely short in the context of human genome evolution and extremely long in the context of the evolution of medical publishing and case reporting. Therefore, the subsequent question arises was LBA really overlooked? In addition to LBA, macroglossia may be a specific symptom of Beckwith-Wiedemann syndrome (syndromic patients) in association with the external ear abnormalities or can present itself as an isolated congenital abnormality (nonsyndromic patients). Macroglossia also can be a component of various other genetic syndromes, or of secondary origin (swollen tongue, tumor, neurofibromatosis, etc.). Genital abnormalities in males are specific for IMAGe syndrome. All such symptoms are detectable by observation and do not require any modern instrumental or imaging medical diagnostic tools. Were they also overlooked?

The hypothesis

The aim of this research was to confirm or to disprove the hypothesis that the instability of the 11p15.5 chromosomal region occurred in the first half of the 19th century and that the event took place in continental Europe. The age of the mutation that leads to LBA and IH is not calculated yet. In fact, while several genes of the 11p15.5 chromosomal region may be involved at the same time (including WT2 gene for Wilms tumor) thus producing various above-mentioned syndromes, it is appropriate to speak of general instability of the region. For genetics, the precise knowledge of when the 11p15.5 region became

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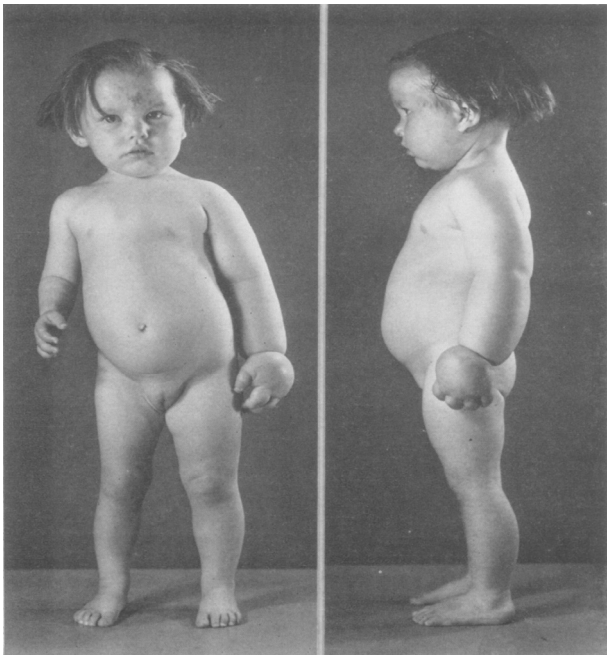

Fig. 1. A case on congenital asymmetry presented by Johnston and Penrose in the Journal of Medical Genetics in 1966 (Johnston AW, Penrose LS. Congenital asymmetry. *J Med Genet* 1966;3(2):77–85. Open Access).

unstable may help in the prognosis of future development of the region, estimates of mutation age and the mutation rate, and for epidemiological purposes. IH was the first region-related disorder described, and our aim was to confirm or to reject the fact that LBA and other syndrome-related visible abnormalities were first described in the 19th century. The second aim was to detect the geographical region where 11p15.5 initially became unstable. We planned to present geneticists with the history of medicine-based rationale of their further analysis of disturbances taking place at the 11p15.5.

Methods

The medical literature from 1557 onwards was searched for any mentioning of possible descriptions of pathological lateral body asymmetry or overgrowth, macroglossia, cryptorchidism, and micropenis. While medical terms such as “hemihypertrophy” or “macroglossia” appeared only in the 19th century, we searched for various phraseological descriptions of the conditions such as, for example, “asymmetry of the two halves of the body”, *macrosomia parziale*, “predominance of development of the left side on the right side”, “congenial inequality of the two halves of the body”, “enlarged tongue”, *linguam tantae magnitudinis*, *lingua magna*, and similar.

The authors analyzed Latin, German, English, French, Russian, Spanish, and Italian sources. While it is already established fact that general treatises on medicine of the 17th, 18th, and 19th centuries did not indicate LBA or IH as separate nosologies, the authors concentrated on treatises on teratology, body asymmetry, and on books of normal, comparative, and pathologic anatomy. The IH or IH-suspicious case reports from the 1830s were studied to assess incidence and geography of LBA.

We analyzed 39 treatises on teratology written from 1557 to 1848, 284 teratological case reports from 1665 to present, 16 books on teratology written since IH was described in 1850 till the 1950s when Russell-Silver syndrome was described, 124 case reports of IH of the same period, 16 early case reports on isolated macroglossia and one M.D. thesis on the subject (1845), six medical books on human body symmetry/asymmetry matters written between 1780 and 1818, four medical museums’ catalogues of anatomical and teratological items, 16

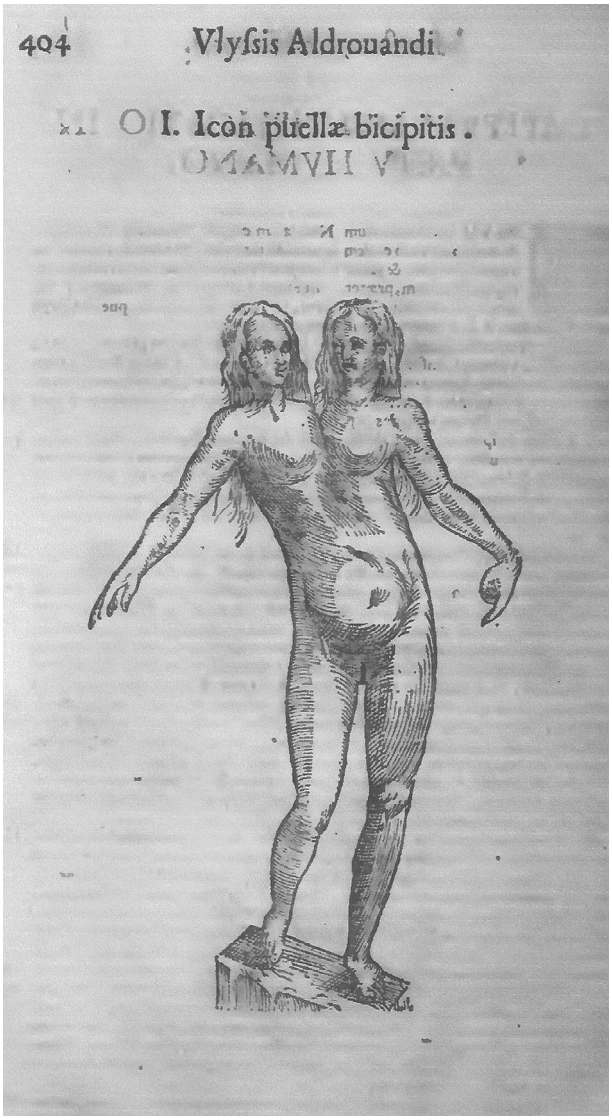

Fig. 2. A case of conjoined twins was described in detail by Ulisse Aldrovandi in the second half of the 16th century. (Ulyssis Aldrouandi. Monstrorum historia cum Paralipomenis historiae omnium animalium. Bologna: Nicolai Tebaldini, 1642).

manuals and treatises on the normal, comparative, and pathological anatomy published from 1591 to the first half of the 19th century, one treatise on gynecology and obstetrics (1579), and five non-medical books on monsters. In sum total, we analyzed 512 publications that appeared before the first 11p15.5-related syndrome was described. (The list of the analyzed sources is presented as a Data Supplement to the current paper).

Results

Medical books on teratology (monsters, *monstruosités*) appeared in the second half of the 16th century and were regularly published since. These books described various cases of abnormalities such as dwarfs, giants, all variations of conjoined twins (double monstrosity, *monstris duplicibus*) (Fig. 2), various facial abnormalities, genital abnormalities including true and pseudo-hermaphroditism (ovotesticular DSDs, *androgynos*), and many other congenital abnormalities. Starting from the first truly medical treatise of Ambroise Paré *De monstres* (1573) [6], more than 30 European authors published books on the subject from the second half of the 16th century to the first half of the 19th century.