Augusto Tamburini (1848-1919) and his Contributions to Acromegaly

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Summary. Acromegaly is a rare disease, similar to gigantism, generally caused by a pituitary adenoma. It was described for the first time by Pierre Marie (1853-1940) in an article published in 1886, although other cases had been reported before, between the 18th and the 19th centuries, also in the 16th century, especially in the field of teratology. In the same article Marie proposed three hypotheses on the pathogenesis of this disease, without involving the pituitary gland. However, in the following years, research intensified all over Europe, other clinical cases were reported, and a debate was opened, thanks to which the cause of acromegaly was identified in a pituitary alteration, and the nature of this alteration was recognized. In the present article this debate is reconstructed, considering the authoritative contributions made by Augusto Tamburini (1848-1919), when he was head of the asylum in Reggio Emilia. Tamburini argued that acromegaly is caused by a hyperfunctioning pituitary adenoma on the basis of anatomical evidence and the experiments carried out by his colleagues, the pathologist Giulio Vassale (1862-1913) and the surgeon Ercole Sacchi, who demonstrated the vital importance of the pituitary gland and its secretions. Tamburini stimulated attention and research on acromegaly in other centres in Italy, among his pupils and colleagues, and his private library, now in the Polytechnical University of Marche in Ancona, represents a precious collection to study this and other aspects of medicine between the 19th and the 20th centuries.

Key words. Acromegaly, Augusto Tamburini, Asylum of Reggio Emilia.

Introduction

Acromegaly is a rare disease, principally characterized by an increase of the volume of extremities, face, hands and feet, and similar to gigantism. In fact, acromegaly and gigantism generally depend on the same tumour, the pituitary adenoma, that causes a hyperfunction of the pituitary gland, i.e., an excessive production of the growth hormone (GH). This condition provokes gigantism before puberty, or acromegaly after puberty, when the epiphyses are already closed.

The neurologist and psychiatrist Pierre Marie (1825-1940), pupil, collaborator, and successor of the great Jean Charcot (1825-1893) at the Salpêtrière of Paris, was the first to describe acromegaly, although it was already known in the ancient world (1, 2). In 1886, Pierre Marie published an article where he coined the name of the disease, using two Greek terms: ácron (extremity), mentioned by Marie himself, and *megalía* from *mégas* (large) (3). In the following years, research on acromegaly and its etiopathogenesis intensified. In 1921 there was a turning point with the discovery of the growth hormone (GH) by the American physician Herbert M. Evans (1882-1971).

The history of acromegaly was reconstructed by Wouter de Herder in two important articles, respectively published in 2009 and 2016 (4-6). The aim of this article is to focus on the pathogenesis of acromegaly and above all on the surrounding debate, that arose after the publication of the article by Marie, presenting Augusto

Tamburini (1848-1919), at that time director of the asylum San Lazzaro in Reggio Emilia, whose contributions have as yet not been given their due importance.

Description of acromegaly

In *La revue de Médecine* of 1886, the French neurologist and psychiatrist Pierre Marie, also known for his research on ankylosing spondylitis, aphasia, multiple sclerosis, and rheumatoid arthritis, published an article on two cases of acromegaly that he came across at the Paris Salpêtrière (3). These cases involved two women of different ages and health conditions, but with similar symptoms: the first one, Fusch, aged 37, was in hospital with severe pains in her head, remained there for a few weeks and then was discharged at her own request; the second one, Héron, aged 54, was in hospital for 16 years, already bedridden, blind and severely debilitated, so much so, that she died a year later, in the summer of 1887. From the detailed description of the two patients Marie deduced that both of them were affected by the same hitherto neglected disease. Moreover, he linked these to five other cases that had been mentioned in literature since the beginning of the 19th century, on which he later returned. He also identified distinct symptoms thanks to which this disease could be distinguished from three others: myxedema or severe hypothyroidism, Virchow's bone leontiasis and deforming osteitis or Paget's disease.

Although Marie found that the two patients had various symptoms in common, including amenorrhea at the onset of the disease, curvature of the spine, neuralgia, polydipsia and polyuria, in a concise and effective way he concluded that the disease that he proposed to call acromegaly is characterized by hypertrophy of the feet, hands and face (p. 333): "Il existe une affection caractérisée surtout par une hypertrophie des pieds, des mains et du visage, que nous proposons d'appeler acromégalie, c'est-à-dire hypertrophie des extrémités." He then added that the extremities are not the only parts of the body affected by this disease, but their hypertrophy is the initial and most characteristic phenomenon.

Previously, other acromegalic patients were described as singular examples, especially in the field of teratology, where the terms *prosopectasia* (dilation of the face) or *macrosomia* (body size exceeding the norm) were sometimes used. Among others, there was a woman hospitalized in Milan, to whom the psychiatrist Andrea Verga (1811-1895) devoted an article in 1864 (7); a peasant from the province of Pavia, aged 37, about whom Cesare Lombroso (1835-1909) wrote a report in 1868 (8); the so-called *bottaro* (barrels' manufacturer), who died in 1808 aged 47: his wax is exposed at the Cattaneo museum of Bologna, and his skeleton was studied by Cesare Taruffi (1821-1902) in 1879 (9). Wouter de Herder compiled a list of twenty cases of acromegaly and gigantism before Marie, reported between the end of the 18th and the 19th centuries, while the first case was the one identified by the physician Johann Wier (1512-1588) in 1567 (10): a woman, who exhibited her gigantic features by travelling from city to city to earn money to support herself and her mother.

The literature of clinical cases, *observationes* or *curationes*, which began in the mid-16th century and further developed until the era of modern medicine (11), could give us other descriptions of acromegalics. One description, written a little before Wier's, is contained in the *Curationes* by Amato Lusitano (1500-1568), the great Jewish Portuguese physician considered to be the founder of this new genre (12, 13). The *Curationes*, collected in seven *Centuriae* and published between 1551 and 1566, contain the histories of patients healed or observed by Amato in the cities where he stayed for various periods of time, from Portugal to Thessaloniki, including Antwerp, Ferrara, Venice, Rome, Pesaro and Ragusa. In the fifth *Centuria*, published in 1560, among the *Curationes* that concern the patients in Pesaro (V 69-100), there is an account about the giant of Senigallia (V 95), a man so called "because he exceeded the average height of one cubit" (14). Amato points out the size of his hands, feet and jaws, as well as his strength. Then he affirms that at the age of twenty the giant fell ill in Senigallia, with ulcers on his feet, and that Guidobaldo II delle Rovere, Duke of Urbin, wanted him to be looked after and treated by the best doctors in Pesaro. Amato shows an uncommon understanding for a man whose strength was as great as his frailty.

Pathogenesis of acromegaly

In the article on acromegaly published in 1886 (3), Pierre Marie was very confident about the specificity of this disease, but also cautious about its aetiology, for which he admitted that there were no reliable data (p. 313): "nous n'avons aucune donnée bien précise." He proposed three different hypotheses - a systemic rheumatic disease, a neurological sympathetic-dependent disease, or a developmental disease - to conclude by reiterating that there was nothing certain about its nature (p. 333): "nous n'avons encore aucune donnée certaine sur la nature de cette maladie."

In this article Marie did not mention the pituitary gland in any way, the same as others who had dealt with acromegaly before, calling it in another way, including Andrea Verga (7), perhaps the first to identify the presence of a pituitary tumour inside the skull, on the sella turcica, of an acromegalic woman who died in 1862, whom he himself had examined in hospital two years earlier, in 1860 (p. 114). In fact, to explain this "unique" disease, Verga rather resorted to Hippocratic humours, to the "ideas of the ancient humoral pathology", writing (p. 116): once menstruation had been suppressed, "the humours threw themselves elsewhere, and first they rushed towards the skin, then they headed on to nourish and develop the whole organism." This is a further proof of the long fortune of the Hipprocratic theory, even if it had already been refuted for a long time.

In the following years, it was however observed that in the dissections of acromegalic corpses the pituitary gland was constantly altered, and the sella turcica, in which the pituitary gland is inserted, was dilated. Therefore, the theory that acromegaly was due to the pituitary gland was supported by physicians and scientists from all over Europe, including Oskar Minkowski (1858-1931), Carl Benda (1857-1932), Roberto Massalongo (1856-1919), and Marie himself, who did further research with his collaborators, also on the corpse of Héron, the acromegalic patient described by him in 1886, who died in 1887 (15-20). However, at that time, very little was known of the nature and function of the pituitary gland, and it was discussed if in acromegaly there was a hypertrophic pituitary gland or a tumour, and also if there was pituitary hyperfunction or hypofunction. In this debate Augusto Tamburini (1848-1919) made an authoritative contribution publishing an article on pathogenesis of acromegaly in German in 1894, in a short version (21), and two articles in Italian, with more details, in 1894 and in 1895, in the *Rivista sperimentale di freniatria,* which were then included in a more ample monograph in 1896 (22).

Born in Ancona from a modest family in 1848, Tamburini managed to study with the help of his older brother Luigi and graduated in medicine in Bologna in 1871. He started his professional activity in Ancona, in the civic hospital San Francesco alle Scale, which included the asylum, but soon he moved to Reggio Emilia, to the San Lazzaro asylum, directed since 1873 by Carlo Livi (1823-1877), one of the fathers of Italian psychiatry, who also founded and edited the *Rivista sperimentale di freniatria*, a leading Italian journal of psychiatry. In 1876 Tamburini left Reggio Emilia for a short time, to teach psychiatry at the University of Pavia and to become director of the Voghera asylum, which Lombroso had wanted before moving to Turin.

The premature death of Livi the following year, in 1877, brought Tamburini, not yet thirty years old, back to Reggio Emilia, where he became director of the local asylum and professor of psychiatry at the university of Modena, as well as editor-in-chief of the *Rivista sperimentale di freniatria*. Although he was offered prestigious positions elsewhere, Tamburini remained at the asylum in Reggio Emilia for over thirty years, promoting it in Italy as an example of excellence both for the assistance and therapy of patients and for research, and placing it among the major centres from all over Europe: Paris, Munich, Vienna, and Berlin. It wasn't until 1906 that Tamburini left Reggio Emilia for Rome, where he took over the chair of psychiatry, previously held by Ezio Sciamanna (1850-1905), and where he founded the clinic of nervous and mental diseases of the Polyclinic Hospital, covering many positions as a member of the Superior Health Council (23, 24).

Tamburini started his article on acromegaly with the presentation of a case, that of Elena Poppi, affected by this disease: hospitalized in the asylum of Reggio Emilia in 1892, aged 38, Elena died a year later, in 1893 (22). Tamburini described in detail the characteristics and symptoms of the patient identified by clinical examination; then observations made on the

sectoral table; finally, the results of the histological examination performed in the laboratory. On the basis of this case and others reported in literature, twenty-four in total that he reviewed, Tamburini concluded that acromegaly is connected to an alteration of the pituitary gland, supporting what he called the "theory of Marie" (p. 36). Moreover, he rightly believed, like Massalongo, that acromegaly and gigantism depend in the same way on a hyperfunctioning pituitary gland. This hyperfunctioning was due to hypertrophy of the pituitary gland, according to Massalongo; in contrast, Tamburini correctly argued that the cause is a tumour of the same gland, predominantly an adenoma.

In any case, he excluded that in these diseases there is a hypofunctioning of the pituitary gland, as Marie proposed, at least in the whole first phase of bone growth, while it could happen at the end, when the patient experiences the cachexia that leads to death. Tamburini admitted that little was known about the pituitary gland and its function, but wrote that "the pituitary gland has a very important function in the organism and is probably destined to develop a special internal secretion product necessary for the animal's life-system" (p. 37). He found support for this crucial assertion in the results of the experiments carried out in the laboratory of his asylum in Reggio Emilia, directed by the pathologist Giulio Vassale (1862-1913), and published by Vassale himself and by the surgeon Ercole Sacchi in the *Rivista sperimentale di freniatria* in 1892 and 1894 (25, 26).

Through the destruction of the pituitary gland in test animals, forty dogs and cats in all, it was possible to demonstrate that the pituitary gland has a vital function for the body: animals without pituitary gland immediately appear to be hindered and quickly come to die; moreover, they recover to some extent and for a short time by injections of pituitary secretion. Vassale and Sacchi developed a new method for reaching the pituitary gland via the palatal vault, without damaging the base of the brain, and destroying it with electrical and chemical cauterization. This method, which Tamburini defined as "elegant" (p. 37), was rapidly adopted everywhere for hypophysectomy studies. In the asylum in Reggio Emilia, therefore, Tamburini's clinical experience and Vassalle's laboratory research effectively worked together.

Conclusions

Tamburini was a leading figure in psychiatry and neurology between the 19th and 20th centuries, famous for his contributions on the localization of brain functions, on hallucinations, also on acromegaly, for legal appraisals, for skills in mental hospital organization, and for initiatives in the field of social medicine. He had many collaborations with colleagues and pupils and influenced research in Italy.

In the *Rivista Sperimentale di Freniatria*, between 1894 and the end of the century, ten articles on acromegaly were published. Two of these, both issued in 1903 - one a report of a clinical case, the other a review of studies - were by Gustavo Modena (1876-1958), a pupil of Tamburini who, after an internship in Vienna, was hired as a doctor and researcher in the asylum in Ancona, in 1902, to be then its director from 1913 to 1939, when he was expelled because of racial laws (27-29). In 1903 Modena himself wrote another article on acromegaly in the first publication of the *Annuario del Manicomio Provinciale di Ancona* (30). It is the description of a clinical case: a 38-year-old patient from Ancona, who died in the asylum, including the report of the autopsy and the results of the histological examination.

Tamburini maintained a close relationship with Ancona, particularly with the asylum of the city, exercising great influence on it. He was part of the scientific commission for the construction of the new asylum in Piano San Lazzaro, inaugurated in 1901 and directed until 1913 by Gaetano Riva (1845-1931), who had been his colleague for twelve years in Reggio Emilia (31). In addition, firstly his nephew Aroldo (1867-1907), son of his brother Luigi who died aged 40 of heart complications following flu, and then, from 1909, his son Arrigo (1878-1943), who died under bombing with other doctors, nurses and numerous patients, worked in the asylum in Ancona. In 1911, Arrigo himself wrote a review of studies on acromegaly in the *Rivista Sperimentale di Freniatria* (32).

To confirm the link with Ancona, that was not lost in time, on the death of Augusto Tamburini, in 1920 his wife Emilia Trebbi donated her husband's private library to the asylum, a precious collection consisting of 3.000 volumes (33). The library of the former asylum of Ancona, which after its closure suffered several losses,

was acquired by the Polytechnical University of Marche in 2018, and subsequently catalogued. Now this library represents an extraordinary tool for studying psychiatry, neurology, and generally medicine between the 19th and 20th centuries.

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