

# Clinical bibliography of Luis Simarro: a patient with brain tumour, 1895

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## ABSTRACT

**Introduction.** Luis Simarro (1851-1921) was a precursor to Spanish neurology, psychiatry, neurohistology, and experimental psychology. He published very few clinical works.

**Methods.** We present an as-yet unknown case report by Luis Simarro, and perform a literature search to identify other clinical works published over his career.

**Results.** The case report concerns a patient who underwent surgery for a brain tumour in 1894, probably one of the first neurosurgical procedures reported in Spain. We identified four other clinical studies published by Simarro, two of which were also unknown until now; the first, published in 1877, describes a case of status epilepticus and the treatment administered.

**Discussion.** From a young age, Simarro displayed mastery of the clinical description of neurological patients and familiarity with the latest research on diseases of the nervous system. From 1885, he comprehensively analysed medical history and examination of neurological patients in order to correctly locate lesions, and addressed in detail the application of the anatomo-clinical method and the understanding of nervous system physiopathology. Simarro's limited clinical bibliography demonstrates his skill as a clinician, with the capacity to use his clinical experience as the basis to train his students.

## KEYWORDS

Bibliography, brain tumour, craniectomy, epilepsy, history of 19th century medicine, Luis Simarro

## Introduction

Luis Simarro (1851-1921) was a precursor to Spanish neurology and psychiatry.<sup>1-3</sup> Lafora considered him the greatest Spanish neurologist and psychiatrist of the second half of the 19th century.<sup>4</sup> He complemented his clinical work with histological research into the nervous system. Today, he is mainly known for showing Cajal the Golgi staining technique<sup>1,2,4,5</sup> and for developing his own staining method using silver salts,<sup>6</sup> which Cajal later simplified and perfected as part of his research into silver staining.<sup>4,7</sup> Simarro's disciples include some of the most distinguished neurologists, psychiatrists, and neurohistologists of 20th-century Spain: Achúcarro,

Lafora, Gayarre, and José Sacristán, among others. As the country's first chair of Experimental Psychology, he also did highly important work in the development of psychology as a science in Spain.<sup>8</sup> However, his clinical knowledge and research was only communicated to a limited extent, as he took little interest in writing and publishing his work.<sup>4,9,10</sup> In fact, none of Simarro's published clinical case reports were known to date.

In this article we present an as-yet unknown case report written by Simarro, and analyse it in the context of the period and against Simarro's other writing. The article concerns a patient who underwent surgery for a brain tumour in 1894, probably one of the first neurosurgical procedures reported in Spain (Figure 1).<sup>11</sup>

## Material and methods

We describe the clinical case published by Luis Simarro in *Revista Clínica* in 1895.<sup>11</sup>

We searched Luis Simarro's complete written works for articles and reports of essentially clinical content. We mainly studied the bibliographies included in biographies and other studies on Simarro,<sup>1,8,12-17</sup> as well as searching for the term "Luis Simarro" in the electronic catalogues of the Spanish National Library (general catalogue and newspaper archives), the Uriach Foundation 1838 archive, the library of the Spanish Royal National Academy of Medicine, and the library of the University of Valencia.

## Results

### Clinical case

The patient was a 54-year-old man with no history of disease. In August 1894 he began experiencing dizziness ("vertigo"), described by the patient as a sensation of faintness lasting less than one minute, with no loss of consciousness and no sensation of motion, accompanied by nausea. These episodes became increasingly frequent, reaching a frequency of one every two-three days. In the targeted medical history interview, he reported that for eight months he had been distracted and hesitant and had experienced memory loss, poor coordination, and slowed speech.

In November, he had had an episode of left-sided leaning gait and poor coordination in the right limbs, accompanied by aphasia. The following day, when he was examined for the first time by Dr Simarro, hemiparesis had resolved, although he continued to display paraphasia and tremor of the head and occasionally of the upper limbs. These neurological alterations fluctuated over the following days and the patient presented wake-sleep rhythm alterations and fluctuating attention. Eye fundus was normal, and the patient presented bradycardia (60 bpm). The patient improved after administration of potassium iodide (2 g/day). On 15 November, he began to report headaches in the left parietal region.

At this point, the possibility of an organic cerebral disorder was considered. Vascular alterations ("arteriosclerosis") were initially considered, but analysis of the cardiac and aortic pulse showed no abnormalities. Nephritis was also ruled out through a urine sediment examination and urine biochemical analysis.

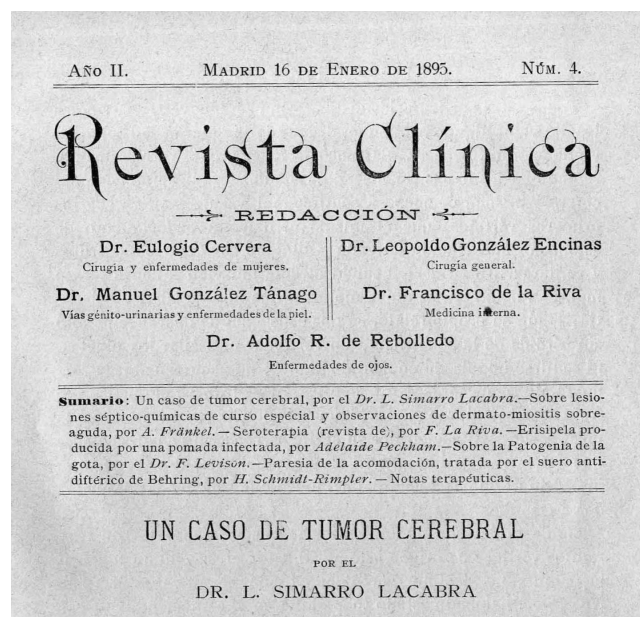
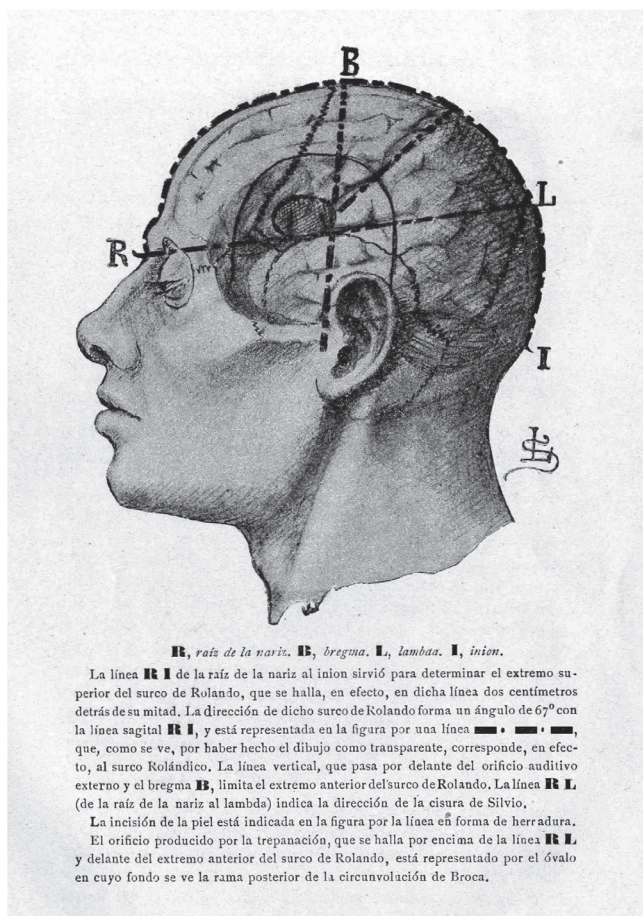


Figure 1. Front page of *Revista Clínica*, with the beginning of Luis Simarro's article.

Symptoms worsened on day 28, with the reduced level of consciousness, aphasia, hemiparesis, and tremor becoming more pronounced. Recordings of the unintentional tremor showed a frequency of four oscillations per second. Potassium iodide dose was increased to 5 g/day, and symptoms improved. However, on 5 December he rapidly worsened, with an apoplectic seizure leaving him in a coma. Temperature was 37.8°C and heart rate was 96 bpm. The patient presented a contracted left pupil, absent pupillary light response bilaterally, and Cheyne-Stokes respiration. He displayed right inferior facial palsy and right hemiparesis (movement only in response to painful stimulus). Hypodermic ether and camphor injections were administered when the Cheyne-Stokes respiration appeared to be endangering his life; antisyphilitic treatment was started with injections of mercuric ammonium chloride, despite the patient having no history of syphilis. He improved once more over the following days, but continued to display stupor, aphasia, and hemiparesis. The patient worsened again on 18 December, displaying Cheyne-Stokes respiration and high temperature.

Brain haemorrhage was ruled out due to presence of apoplectiform attacks. The sudden exacerbations were interpreted as epileptic equivalents secondary to a brain



**Figure 2.** Original drawing by Luis Simarro (signed LS) demonstrating the technique used for the localisation of the Sylvian and Rolandic fissures and the inferior frontal gyrus. It also indicates the incision made in the scalp.

The legend reads:

**R**, root of the nose. **B**, bregma. **L**, lambda. **I**, inion.

Line **RI** from the root of the nose to the inion was used to determine the superior end of the Rolandic fissure, which is effectively located two centimetres behind the halfway point of that line. The Rolandic fissure forms a  $67^\circ$  angle with sagittal line **RI**, and is represented by a dash-dot line. Due to the transparency of the cranium in this drawing, we can see that said line corresponds to the Rolandic fissure. The vertical line, passing in front of the ear and to the Bregma **B**, meets the anterior end of the Rolandic fissure. Line **RL** (from the root of the nose to the lambda), indicates the direction of the Sylvian fissure.

The incision on the skin is represented as a horseshoe-shaped line.

The orifice resulting from trepanation, above line **RL** and anterior to the Rolandic fissure, is represented by the oval containing the posterior branch of the Broca area.

tumour. On 23 December, the right limbs became rigid during one of these episodes, displaying “epileptoid tremor, like small, fast, clonic contractions, which could be provoked by passive movements.” For the first time, eye fundus examination revealed dilated veins. The

patient had a temperature of  $37.9^\circ\text{C}$  and a heart rate of 96 bpm.

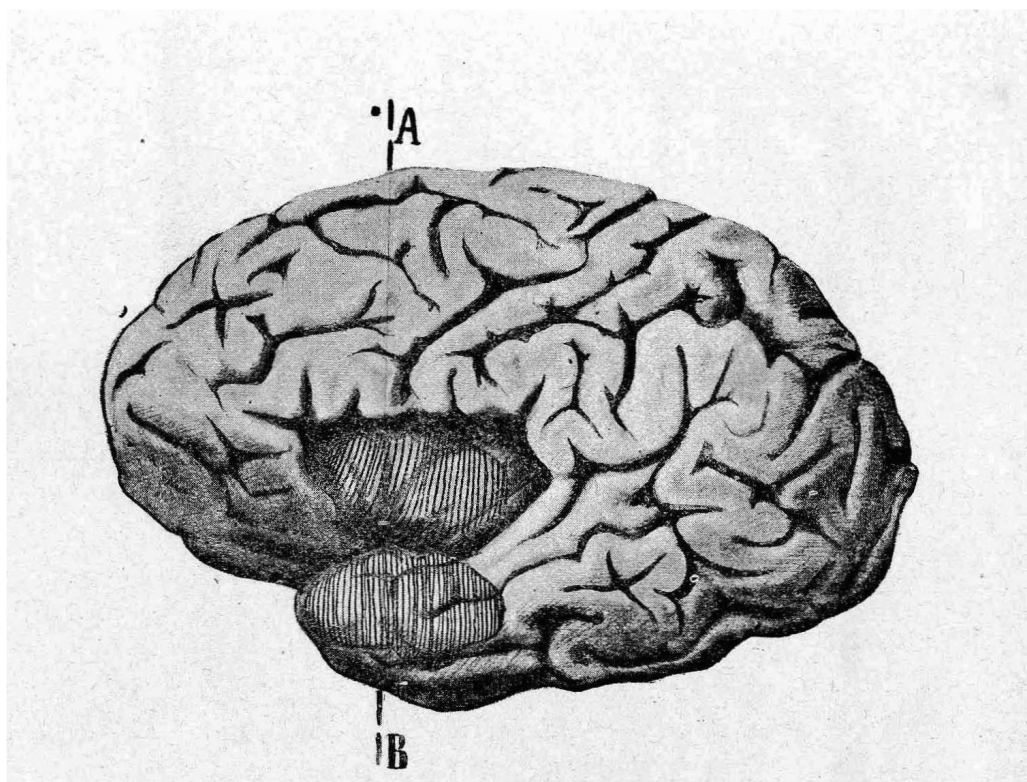
With the patient in a coma, it was decided that Dr Sanmartín would perform trepanation the following day. Chloroform was unnecessary due to the patient’s coma state. After the surgical site was washed, the Rolandic and Sylvian fissures were marked using external reference points and anthropometric measurement. Trepanation was performed immediately anterior to the inferior end of the Rolandic fissure, along the line indicating the direction of the Sylvian fissure (Figure 2). Surgery aimed to uncover the posterior branch of the “M” sign constituting the inferior frontal gyrus. No pulsation was detected upon exposing the dura mater, although a pulse did become apparent when the incision was made. When the inferior frontal gyrus was exposed, there was no external sign of any structural anomaly, except that it herniated into the dura and did not display pulsation. Three punctures were performed, with no positive result; the brain then began pulsing, for which reason the exploration in search of the tumour was discontinued, as intracranial pressure appeared to have been sufficiently relieved.

However, the patient’s symptoms did not improve. Coma continued; the patient had fever and a heart rate of 130 bpm. The following day, a trocar was inserted 6 cm; 15 cc of yellowish transparent liquid was withdrawn. Floating in the liquid was a white membrane, also transparent; echinococcus was ruled out. After the trocar insertion the coma, Cheyne-Stokes respiration, and seizures ceased, and pupillary light response was restored.

On 28 December, the patient presented a similar exacerbation; he died on 3 January.

Autopsy was performed on the cranium only. The gyri of the left hemisphere displayed pronounced flattening; the veins were highly dilated and the entire brain was engorged with blood. Two tumours were identified (Figure 3). The first, located in the white matter below the insula of Reil, had an oval lens shape (52 mm anteroposterior diameter, 35 mm vertically, 11 mm thick). The tumour was soft and somewhat friable; on the anterior end was a near-spherical cystic cavity of around 20 mm diameter, containing a yellowish liquid similar to that extracted by the trocar insertion. Although it was not encapsulated, it was clearly delimited from the surrounding nervous tissue. The other tumour was located on the inferior edge of the “sphenoidal lobe” (sic); it measured 38 mm





**Figure 3A.** Observational drawing of the patient's brain. Lateral view; operculum removed and temporal lobe depressed to show the insula of Reil; subcortical tumours are shown with shading.

vertically, with an anteroposterior diameter of 57 mm and a thickness of 37 mm. The tumour was hard, scirrhou, and lobulated, and was not encapsulated but was very well delimited; the surrounding tissue (half of the sphenoidal lobe) was softened.

The article ends with the words "To be continued" in parentheses, although no further articles were published in the following editions of the journal.

#### Clinical bibliography of Luis Simarro

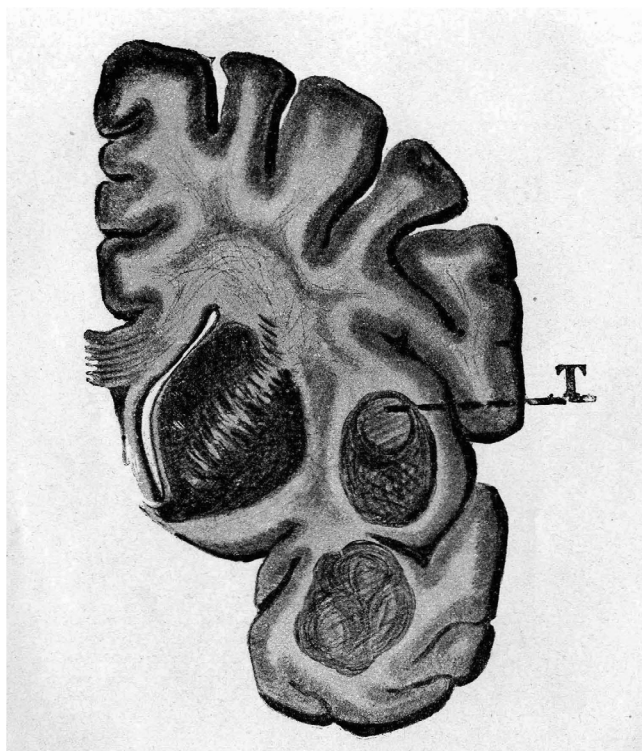
A search for published works written by Simarro identified only four articles of clearly clinical content, besides the case report discussed in these pages. He published an article on epilepsy in 1877, shortly after starting to work at Hospital de la Princesa.<sup>18</sup> In 1885, he published an article entitled "De los reflejos espinales" ("On spinal reflexes") in *Revista Internacional de Ciencias*

*Médicas*; while it was not possible to locate the text in the Spanish National Library's Collective Catalogue of Periodical Publications, its conclusions are reproduced elsewhere.<sup>19</sup> With José María Escuder and Jaime Vera, he co-authored a comprehensive report on the mental health of the member of Parliament Martín Larios y Larios.<sup>20</sup> Finally, he wrote a chapter in the "Vademécum clínico-terapéutico" ("Clinical and therapeutic handbook") on diseases of the nervous system.<sup>21</sup>

#### Discussion

##### Analysis of the clinical case

The case report recounts a good neurological evaluation of a critical patient, given the limitations of the time, leading to acceptable localisation and identification of the lesion. The exploratory use of specific techniques such as ophthalmoscopy and tremor recording is noteworthy.



**Figure 3B.** Observational drawing of the patient's brain. Coronal section showing the tumours and the path of the trocar into the cystic area of the subinsular tumour.

The patient initially presented ill-defined symptoms of dizziness. While reaching a clear diagnosis is difficult, we believe that he may have had insular epileptic seizures, given the location of the tumour below the left insula. This hypothesis is supported by the stereotyped episodes, with progressively increasing frequency potentially due to tumour growth, the short duration, and the presence of such vegetative symptoms as nausea. The episodes cannot be attributed to orthostatic hypotension or paroxysmal vertigo due to the absence of a positional trigger factor.

Three months later, he displayed clear focal left cortical symptoms: aphasia and hemiparesis (possibly due to compression of the internal capsule). However, these symptoms were initially transient, and later intermittent or fluctuating, accompanied by confusional symptoms and altered sleep-wake rhythm. Having established, based on these details, that the patient had an organic brain disorder, Simarro rules out ischaemic stroke (arteriosclerosis), although this is based on limited evidence

(evaluation of pulse). The patient's confusional state leads Simarro to consider a metabolic disorder; he rules out kidney disease ("nephritis") due to normal findings from urine sedimentation and biochemical analysis, the only available means of studying kidney function at the time. He also rules out cerebral haemorrhage on account of the course of the symptoms, which features acute relapses.

Simarro records the patient's tremor, which appears at rest and affects mainly the head and to a lesser extent the upper limbs, finding a frequency of 4 Hz. This may be parkinsonian tremor caused by compression of the basal ganglia.

The presence of headache and the progressive course are suggestive of brain tumour. Ophthalmoscope monitoring of the eye fundus was performed from the time of the first examination; no anomalies were detected until several weeks after the initial consultation. Simarro's correct interpretation of the acute (apoplectiform) episodes as epileptic equivalents due to focal epileptic seizures also points to brain tumour. This interpretation was confirmed several days later by the onset of clear clonic seizures in the right arm and leg. Rostrocaudal deterioration is accompanied by Cheyne-Stokes respiration and contracted left pupil, which is indicative of diencephalic involvement. The appearance of fever and tachycardia may be secondary to aspiration pneumonia due to the low level of consciousness. Central fever is another possible explanation. Simarro does not discuss the possibility of brain abscess, although the trocar insertion in search of the lesion following craniectomy suggests that that diagnosis was considered; this was probably one of the few diagnostic possibilities that would have resulted in favourable progression.

The treatments used reflect the therapeutic limitations of the late 19th century. Potassium iodide was used to treat tertiary syphilis, and especially the syphilitic gumma. Syphilis was one of the most frequently diagnosed neurological diseases in the latter half of the 19th century, and it is logical that this would be included in empirical treatment for an expansive cerebral process, despite Simarro acknowledging the absence of data supporting diagnosis of syphilis. Following the failure of potassium iodide, mercury salts were added; this combined treatment was also unsuccessful. Hypodermic injection of ether and camphor was used to stimulate circulation and respiration if these functions collapsed due to various acute conditions.

The progression to coma led to the decision to perform craniectomy. The patient's condition meant that anaesthesia with chloroform was unnecessary. Without a doubt, this is one of the first neurosurgical procedures reported in Spain; the development of modern neurosurgery began in the latter part of the 19th century. Increasing understanding of cerebral localisation in the second half of the 19th century enabled clinicians to establish the location of cerebral lesions. Cranial procedures were performed by general surgeons with support from specialists in diseases of the nervous system.<sup>22</sup> The early procedures took place in Great Britain: in the 1870s, William Macewen (1848-1924) extirpated a convexity meningioma and performed brain abscess and subdural haematoma drains. Victor Horsley (1857-1916) was the first person to resect a spinal tumour, in 1887. In Spain, Alejandro Planellas operated on a patient with head trauma in 1881, in Barcelona. In Madrid, Federico Rubio y Galí (1827-1902), Eulogio Cervera Ruiz (1855-1916), and José Ribera Sans (1852-1912) also performed craniectomies on patients with Jacksonian epilepsy and to evacuate abscesses, beginning in 1890.<sup>22</sup> The surgeon who operated on Simarro's patient ("Sanmartín") is in all likelihood Dr Alejandro San Martín (1847-1908), chair of surgical pathology in Madrid from 1882; he was also relatively experienced in the area of cranial surgery. One of his best known contributions was the treatment of trigeminal neuralgia by extirpating the Gasserian ganglion via a sphenoidal excision.<sup>23</sup> As Simarro's article explains, neurosurgical planning was based on the cranial projection of cerebral structures, and relied on the use of external reference points and anthropometric measurements. Slocker de la Pola<sup>24</sup> had published his thesis on the subject just a year earlier. Simarro would without a doubt have been involved in the surgery and in intraoperative decision making. The procedure confirmed that the patient had increased intracranial pressure, as shown by the herniation of the inferior frontal gyrus when the dura mater was opened and by the absence of pulsation. However, as the superficial exploration did not locate the tumour, they decided to perform exploratory punctures, without success. The procedure was concluded when they observed that brain pulsation was restored, inferring that the intracranial hypertension had resolved. It seems that not having located the tumour dissuaded them from continuing the intervention into an eloquent brain region. However, since the poor clinical situation persisted, they opted to

perform a trocar insertion the following day; they were able to extract 15 cc of liquid, which enabled them to rule out a brain abscess and improved the patient's condition by decreasing the intracranial pressure. However, this could be no more than a transient palliative measure, as the disease would most likely progress to death if the tumour was not resected.

Autopsy of the cranium revealed two independent tumours: one below the insula and the other in the temporal lobe. Both were well delimited from the nervous tissue, suggesting cerebral metastasis, and contained necrotic areas. Survival time (four months from the appearance of the first symptom attributable to the tumour) is consistent with what we would expect for cerebral metastasis. None of the clinical details shed light on which was the primary tumour, and no autopsy was performed. We imagine that Simarro intended to perform a microscopy study of the tumours and publish his findings in the next edition of the journal, hence the conclusion "to be continued." This was not the first time that Simarro left an article unfinished, at a time when it was customary to publish works in fragments over successive editions of a journal; in 1878, he published the first part of "Descendencia y darwinismo" ("Inheritance and Darwinism"), which was never continued.<sup>12</sup>

#### Clinical bibliography of Luis Simarro

Given the limited number of clinical works Simarro wrote, it is even more extraordinary that, as an older man, he should report an isolated clinical case. Many of Simarro's works are transcriptions of lectures or courses he gave, of which many were published in the gazette of the Institución Libre de Enseñanza (Free Institute of Learning; ILE), where he also reported on his time in Paris between 1880 and 1885. This demonstrates Simarro's strong commitment to the ILE. His works also include prologues to books; this can only be interpreted as a sense of personal duty to the authors or translators. He also published a number of articles in the general press. Simarro has always been said to have produced little written work,<sup>4,9</sup> and his limited impact in Spanish science has frequently been attributed to this. Certainly, his celebrity at the time and his hugely important contribution to the development of Spanish science are not matched by his recognition today, although his work has become better known in recent decades. According to Luis de Zulueta, Simarro "couldn't be bothered to write,"<sup>10</sup> although it would seem that when a subject



did interest him, he did not hesitate to dedicate the necessary time. The most striking example is his book “El proceso Ferrer y la opinión europea” (“The Ferrer trial and European opinion”), a 650-page volume on Ferrer Guardia’s conviction and sentencing to death, which Simarro actively opposed.<sup>25</sup> Luis Simarro was highly involved in the debate around the legal status of mental illness, which was at the heart of the controversy surrounding the Galeote case, and published numerous articles on the subject.<sup>26–28</sup> In 1886 he was appointed to a commission responsible for drafting a bill establishing protection measures against the criminally insane and a legal basis for the construction of an asylum for these individuals. We can also point to the report he drafted on his staining technique. It was published simultaneously in two journals: Cajal’s *Revista Trimestral Micrográfica*, and *Revista Iberoamericana de Ciencias Médicas*, under the directorship of his friend Federico Rubio.<sup>29,6</sup>

Despite his later disinterest, Simarro was involved in scientific writing at the beginning of his career. As a student in Valencia (1872–1873) he promoted the publication of a volume of clinical cases treated at the hospital there.<sup>30</sup> In 1877, he presented a case of status epilepticus, demonstrating extensive knowledge of the French neurological literature and stating his admiration for Charcot.<sup>18</sup> In the article, he defends Bourneville’s idea that measuring body temperature enables differentiation between epileptic seizures and haemorrhagic or ischaemic stroke (“acute brain softening”), even going so far as to argue that “any possibility of an epileptic seizure would be ruled out” if the patient had had a low temperature, despite his marvellously detailed description of the status. He uses amyl nitrite, which he had previously used in five other cases, for acute treatment of status epilepticus, and bromide for chronic care.

In his article on spinal reflexes, published upon his return from Paris in 1885, Simarro discusses various alterations of the patellar reflex, showing the relevance of the test in lesion localisation, depending on the accompanying examination findings.<sup>19</sup>

The report on Martín Larios is not truly a clinical publication, as it was not printed for dissemination among physicians, although it does represent a good example of a highly professional neurological and psychiatric assessment of a patient at an early time in the development of Spanish neurology. The report has been analysed in previous articles.<sup>31,32</sup> It is noteworthy

for the thorough, systematic approach to medical history and neurological and psychiatric examination. The exploratory techniques available at the time were used in the Larios report. The authors analyse in detail the possible localisation of the alterations identified, with certain errors attributable to the limited scope of neurological understanding at the time. Simarro is clearly influenced by the French school: the authors apply the anatomo-clinical method and the concepts of “hereditary neuropathy” and degeneration.<sup>31</sup>

Beginning in 1875, Simarro was an instructor at the Escuela Práctica Libre de Medicina y Cirugía (Free Practical School of Medicine and Surgery) in Madrid, a centre with a positivist, physiopathological approach.<sup>33</sup> Between 1877 and 1879, he worked at the Santa Isabel insane asylum in Leganés. There is evidence that Simarro’s diagnostic work there also drew on the French psychiatric thought of the moment.<sup>34</sup> He began to perform post mortem examinations on mentally ill patients who died at the institution. This was probably an early attempt by Simarro to bring anatomo-clinical and histopathological methods to the study of mental illness. However, within a year he was reprimanded by the director of the centre; Simarro left the asylum the following day to return to his former employment at Hospital de la Princesa.<sup>34</sup> Shortly before the turn of the century, Simarro created a small, free, and highly practical teaching centre in collaboration with Juan Madinaveitia, who worked at the Hospital General de Madrid. Nicolás Achúcarro, Gonzalo Rodríguez Lafora, Miguel Gayarre (who later became director of the Ciempozuelos insane asylum), and the brothers Juan de Dios and José Miguel Sacristán all completed their initial training there. Students attended Madinaveitia’s rooms at the hospital for instruction on the anatomo-clinical method and physiopathological medicine, which Madinaveitia had become familiar with in Germany. In the afternoons, they worked in Simarro and Madinaveitia’s laboratory on Calle General Oraá, where they learned histological techniques using samples taken from Madinaveitia and Gayarre’s autopsies. Achúcarro, Lafora, and José Miguel Sacristán completed their anatomo-clinical training in Germany, with Kraepelin and Alzheimer, focusing on the histopathology of mental illness. Some students were funded by the Board for Advanced Studies, on which Simarro had sat since it was established.<sup>35,36</sup> As the volume of Simarro’s clinical and research work decreased, his school was merged with Cajal’s.<sup>4</sup>

“Diseases of the nervous system,”<sup>21</sup> Simarro’s contribution to the Clinical and Therapeutic Handbook, should be interpreted in the context of this teaching group. The authors of the clinical chapters include two of his closest friends and collaborators, Juan Madinaveitia and Miguel Gayarre. Simarro’s chapter addresses general pathology of the nervous system with a highly practical approach. His explanation of neurological examination and alterations reveals his great clinical experience and his talent as an educator.

We believe that the publication of the case report discussed above was motivated by the anatomo-clinical interest and the importance of the case, as one of the first neurosurgical procedures performed in Spain. There may also have been a sense of personal duty to the journal’s editor Eulogio Cervera Ruíz (1855-1916) and to other contributors including Madinaveitia, Gayarre, and Cajal (although the latter never published any articles in the journal). Biographies of Simarro show no direct relationship between him and Cervera, although we suspect that they would have been acquainted, as their careers coincide several times. Cervera completed his medical training in Madrid in 1875, two years after Simarro, and, also like Simarro, was born in Valencia (Torrente). Having been head of department at the Instituto Rubio, it is highly likely that he would have known Simarro through Federico Rubio y Galí, a close friend and colleague of Simarro’s at the ILE and the Escuela Práctica Libre de Medicina y Cirugía. *Revista Clínica* was published for only three years (1894-1896), having been established as an outlet for case reports from the Cervera polyclinic, founded by Eulogio Cervera in 1894, and for notes on treatments and literature reviews.<sup>37</sup>

### Conflicts of interest

No funding was received for the present study.

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