Malaria Fever Therapy for General Paralysis of the Insane: A Historical Cohort Study

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Keywords

Dementia · General paralysis of the insane · History of neurology · Malaria fever therapy · Neuropsychiatry · Neurosyphilis

Abstract

Background/Aims: This year marks the 100th anniversary of the first malaria fever treatment (MFT) given to patients with general paralysis of the insane (GPI) by the Austrian psychiatrist and later Nobel laureate, Julius Wagner-Jauregg. In 1921 Wagner-Jauregg reported an impressive therapeutic success of MFT and it became the standard treatment for GPI worldwide. In this study, MFT practice in the Dutch Vincent van Gogh psychiatric hospital in GPI patients who had been admitted in the period 1924–1954 is explored. **Methods:** To identify patients with GPI, cause-of-death statistics was used. Data on MFT were retrieved from annual hospital reports and individual patient records. **Results:** Data on MFT were mentioned in the records of 43 out of 105 GPI patients. MFT was practiced in a wide range of patients with GPI, including those with disease duration of more than 1 year, up to 70 years of age, and those with a broad array of symptoms and comorbidities, such as (syphilitic) cardiac disease. Inocu-

lation with malaria was done by patient-to-patient transmission of infected blood. **Conclusions:** MFT practice and mortality rates in MFT-treated patients correspond to similar findings worldwide. MFT was well tolerated and MFT-treated patients had a significantly longer survival.

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Introduction

General paralysis of the insane (GPI), also designated as “general paralysis” and “dementia paralytica”, is a chronic syphilitic meningoencephalitis that causes the progressive degeneration of the central nervous system and a general dissolution of mental and physical capacities. Isolated reports of this previously undescribed and uniformly fatal form of insanity first arose in the late 18th century [1].

On June 14, 1917, Julius Wagner-Jauregg (1857–1940) performed his first experiment on intentionally induced malaria for the treatment of patients with GPI in Vienna [2]. In 1921, he reported an impressive therapeutic success and thereafter this became the standard treatment for GPI worldwide. In 1927, Wagner-Jauregg was the first psychi-

atrist to be awarded the Nobel Prize of Medicine or Physiology “for his discovery of the therapeutic value of malaria inoculation in the treatment of dementia paralytica” [2]. Despite the reported beneficial effect of malaria fever treatment (MFT), its risks were considerable. Treatment mortality rates varied from 4, 3% [3] to 20% [4–8].

While in Denmark introduction of MFT was hampered by the risk of reintroducing an extinct disease [7], *Plasmodium vivax* tertian malaria was still an endemic in the Netherlands [9]. Already in 1921, K.H. Bouman (Dutch neuropsychiatrist) was the first to treat neurosyphilitic patients with MFT in the Netherlands [8]. In 1922, promising results were reported [10] and soon afterwards, MFT was introduced in the treatment of psychiatric patients in Venray, the Netherlands.

Although research on the history of MFT in GPI patients has been performed in the United States [11–13], Britain [14], Scotland [6], and Denmark [7], no historic study on MFT in GPI patients in a psychiatric hospital in the Netherlands has as yet been reported. Therefore, in this retrospective cohort study, we investigated MFT-practice in GPI patients who were admitted during the period 1924–1954 and died while hospitalized in a psychiatric hospital in the Netherlands.

Methods

For this study, the practice of MFT was investigated in patients with an established diagnosis of GPI, who had been admitted during the period 1924–1954 and died while hospitalized in either the psychiatric hospital for male or for female patients in Venray, the Netherlands, at present together known as Vincent van Gogh Institute for Psychiatry (VvGI).

To identify patients with GPI, cause-of-death statistics collected over the period 1924–1954, as stored in the institute’s historical archive, located at the Social Historical Centre of Limburg in Maastricht, was used. Individual medical case records of GPI patients, collected at the same archive, were scrutinized.

Data on MFT were retrieved from annual hospital reports and individual patient records. The admission age of first hospitalization was used. For each patient, data on the first application of MFT were analyzed. In case the date of inoculation was not mentioned in the medical record, it was set at 14 days before the first fever spike was recorded. Epidemiological data and clinical course of all patients were collected to analyze selection criteria and treatment results. Influence of MFT on survival was analyzed with a Kaplan-Meier survival curve.

Data were anonymized before evaluation. Study approval was obtained by the Vincent van Gogh Institutional Review Board (Number: 13.034).

To illustrate the MFT procedure in GPI, 2 case descriptions are presented.

Fig. 1. Number of general paralysis of the insane (GPI) patients deceased during 1924–1957 based on cause-of-death statistics, number of patients whose clinical record was available, and number of patients with malaria fever therapy (MFT+) and without (MFT–).

Results

Data from the Annual Hospital Reports

Annual reports for the years 1929–1954, except those from 1936 to 1950, were available for evaluation. In those years, approximately 750 male and 750 female patients resided in the psychiatric hospital and each year approximately 140 male and 130 female patients were admitted.

Data from the Cause-of-Death Registers

During the period 1924–1957, 180 patients (137 men, 43 women) with an established diagnosis of GPI died while in the hospital.

Patient Records

The clinical records of 105 (58%) (91 men and 14 women) of the total of 180 GPI patients were available for analysis. Of these 105 patients, 10 (9.5%) had been admitted more than once (9 men, 1 woman). Data on MFT were mentioned in the records of 43 out of 105 patients (41%: 39 men; 4 women; Fig. 1). Two patients received MFT twice. In this study, only data on the first MFT were analyzed.

MFT Procedure

No differences were found with respect to disease duration before admission, earlier MFT, and other anti-neurosyphilitic treatments in patients with and without

Table 1. Characteristics of patients with general paralysis of the insane treated with malaria fever therapy (MFT+) or without (MFT–)

	MFT+ (<i>n</i> = 43)	MFT– (<i>n</i> = 62)
Gender, female, <i>n</i> (%)	4 (9.3)	10 (16.1)
Age at admission, mean (range)	48.0 (31.5–69.0)	51.9 (32.9–82.1)
With known duration of disease before admission, <i>n</i> (%)	34 (79)	49 (79)
Duration of disease before admission, years, mean (range); median	1.6 (0.1–8.0); 1.0	2.0 (0.1–9.0); 1.0
Treated for (neuro) syphilis before current admission, <i>n</i> (%)	16 (37)	25 (40)
None or unknown earlier treatments, <i>n</i> (%)	27 (63)	37 (60)
Earlier MFT treatment, <i>n</i> (%)	4 (9)	7 (11)
Symptoms, <i>n</i> (%)		
Abnormal mood fluctuations	17 (40)	21 (34)
Depression	9 (21)	16 (26)
Mania	33 (77)	40 (65)
Dementia	33 (77)	52 (84)
Speech disorders	38 (88)	43 (69)
Tremors	7 (16)	13 (21)
Abnormal pupil (reflexes)	19 (44)	30 (48)
Age at death, mean (range)	52.4 (33.8–70.5)	54.1 (33.1–82.1)
Survival from admission to death, years, mean (range); median	4.3 (0.0–25.4); 1.8	2.1 (0.0–20.6); 0.9
Duration of disease until death, years, mean (range); median	6.5 (0.2–25.6); 4.4	3.8 (0.2–21.2); 3.0

MFT. Details on patient characteristics are presented in Table 1.

Age of MFT-treated patients varied from 31.5 to 69.0 years (*n* = 43; mean 48.0 years) vs. 32.9–82.1 years (*n* = 62; mean 51.9 years) of untreated patients.

Pre-treatment screening comprised a thorough clinical examination, laboratory tests, and X-ray of the chest. In 5 of these patients, an enlarged configuration of the ascending aorta was noticed, suggestive of a syphilitic aortic aneurysm. One additional MFT-treated patient had a medical history of a syphilitic aortic aneurysm, but the data on the chest X-ray of this patient are unknown.

The interval between admission and the start of MFT (known for 42 patients) ranged from 2 days to 6 months. Thirty patients were treated with MFT within one month after admission. Patients were inoculated by subcutaneous injection between the shoulder blades with 1–3 cm³ blood containing malaria parasites. Infected blood was usually obtained from another patient who underwent MFT. In none of the medical records, transmission of malaria by infected mosquitoes was noted. For 9 patients, the *Plasmodium* species was recorded: 7 were treated with *P. malariae* and 2 with *P. vivax*.

Typically, the first febrile attack occurred after an incubation period of about 2 weeks. After 8–12 paroxysms of high fever (39–40°C = 102–104°F) in a period of 10–14 days, patients were treated with quinine sulphate to

terminate the malaria infection. In 2 patients, MFT fever spikes discontinued spontaneously. Following malaria treatment with quinine, patients received additional anti-syphilitic treatment with metals like arsenic and bismuth.

MFT Complications

In 14 patients, premature termination of MFT was recorded and 4 of those died within one month of malaria inoculation. In 13 cases, one or more reasons for premature termination were mentioned: occurrence of daily fever spikes without fever-free, restorative days (*n* = 5), diarrhea (*n* = 3), anemia (*n* = 2), exhaustion (*n* = 2), pneumonia (*n* = 1), jaundice (*n* = 1), and/or pyelocystitis (*n* = 1).

Survival and Cause of Death

Patients treated with MFT had a significantly longer survival after admission (*p* = 0.02; log-rank test; Fig. 2).

Cause of death was recorded in 24 (56%) MFT-treated patients and in 33 (53%) non-MFT-treated patients. In both groups, pneumonia, epileptic seizures, and pressure ulcers were contributing factors to the cause of most deaths. One non-MFT-treated patient died from malaria. It is not known whether malaria in this case was a relapse of a prior spontaneous infection or due to earlier undocumented MFT. Details are presented in Table 2.

Case Descriptions

Case A

A 43-year-old married man was admitted to the hospital in June 1938 because of progressive confusion and aggressive impulsive behavior. His medical history revealed a short episode of confusion 2 years earlier.

On admission, he showed confused, agitated, and destructive behaviors with frequent shouting, singing, and spitting. He had a reduced need for sleep and persistently refused food and medical examination. Neurological observation demonstrated gait disturbances, but no obvious motor or sensory deficits.

Routine laboratory testing revealed a positive Wassermann test in blood and cerebrospinal fluid and the diagnosis of GPI was made. Subsequently, the patient was inoculated with malaria parasites and he developed daily fever spikes. After 9 fever spikes, the malaria infection was treated with quinine. Following MFT, salvarsan and bismogenol were prescribed. His physical condition recovered rapidly and, although he occasionally showed aggressiveness toward his wife, gradually some improvement of his mental condition was noted too. Since his mental and neurological states were sufficiently improved, he was discharged 9 months after admission.

One year later, the patient was readmitted. His sister wrote in a letter to his physician that he had been functioning rather well until the unexpected death of his wife. Thereafter, he became frightened and depressed. Psychiatric examination at readmittance revealed a depression with suicidal ideations and visual hallucinations. He was confused, restless, and unable to communicate and died within 4 weeks after readmission, due to physical and mental exhaustion.

Case B

In August 1938, a 58-year-old barkeeper, who had been a widower for nearly 10 years, was admitted to the hospital. For over 1 year, he progressively developed depressive symptoms and became introverted, often mumbling to himself. Occasionally, there were aggressive outbursts during which he chased his customers out of his bar.

Mental status examination on admission revealed a depressed man with suicidal ideations and a gloomy appearance. He frequently showed episodes with intensive crying and fears of financial ruin. Mild psychomotor retardation was noticed, but memory and intellectual function were intact. His behavior was characterized by paranoia without reporting hallucinatory experiences.

Fig. 2. Survival after admission (Kaplan-Meier) per treatment category. Curves shown till 8 years follow-up. Malaria fever therapy (MFT+) and MFT- survival differ significantly ($p = 0.02$; log-rank test).

Table 2. Causes of death of patients with general paralysis of the insane treated with malaria fever therapy (MFT+) or without (MFT-)

	MFT+	MFT-	Total
Number with cause of death mentioned in files	24	33	57
Epileptic insults, <i>n</i> (%)	7 (29)	10 (30)	17 (25)
Pneumonia, <i>n</i> (%)	7 (29)	9 (27)	16 (28)
Other infections, <i>n</i> (%)	2 (8)	6 (18)	8 (14)
Decubital lesions, <i>n</i> (%)	3 (13)	4 (12)	7 (12)
Heart failure, <i>n</i> (%)	2 (8)	5 (15)	7 (12)
MFT, <i>n</i> (%)	3 (13)		3 (5)
Haematemesis, <i>n</i> (%)	1 (4)	1 (3)	2 (4)
Jaundice, <i>n</i> (%)	2 (8)		2 (4)
Nephritis, <i>n</i> (%)	1 (4)	1 (3)	2 (4)
Cerebro vascular accident, <i>n</i> (%)		2 (6)	2 (4)
Gastric cancer, <i>n</i> (%)	1 (4)		1 (2)
Malaria, <i>n</i> (%)		1 (3)	1 (2)

At medical examination, his pupils were regular, equal, and slowly reacting to light. Achilles tendon reflexes were absent bilaterally. Laboratory tests demonstrated a positive Wassermann reaction in blood (+7 on a scale from 0 to 10) and cerebrospinal fluid (+8 on a scale from 0 to 10).

A diagnosis of GPI was made and MFT was started within 1 month of admission. The patient developed several spikes of high fever. Due to severe anemia and decubital lesions, MFT had to be discontinued prematurely.

For several months, he remained depressive and severely restricted in performing the activities of daily living. Four months after MFT, however, his mood changed and he became manic with delusions of grandeur. In the following months, he showed several mood swings. In April 1940, he was discharged on parole on request of his family.

Two years later, the patient became confused and agitated. He quarreled with his children and customers at daytime and wandered the streets at night. His general physician requested readmission and suggested retreatment with MFT because of the partial success ascribed to the first treatment. On readmission, the patient was very confused and disoriented. Although his speech was severely dysarthric, he was able to express his delusional belief that all close to him had deceased. His mood changed rapidly from euphoric to depressive and periodically he was very anxious. Within 2 weeks of admission, MFT was started and the patient was subcutaneously injected with 3 mL blood containing *P. malariae* (quartan malaria). Fourteen days later, regular spikes of fever started. Severe anemia and heart failure necessitated treatment with digitalis. After 6 fever spikes within 2 weeks, the patient became exhausted. MFT was terminated with quinine and he received neo-salvarsan and bismogenol. His clinical condition remained unchanged until his death one year later. No specific cause of death was recorded in the case notes.

Discussion

To the best of our knowledge, this paper is the first historical study on MFT in GPI in a psychiatric hospital in the Netherlands. In this cohort study focusing on MFT in the period 1924–1957, MFT practice was analyzed in 43 patients with GPI. Although MFT has been used for thousands of patients across the world and has greatly contributed to the knowledge of malariology [8], its value for treatment of GPI remains doubtful. The reported magnitude of success of MFT was highly variable and the rapid and widespread acceptance of this therapy probably reflects the absence of an effective treatment for this disease at the time [5].

Comparative, well-controlled, trials of MFT versus standard therapy, or MFT versus other types of fever have not been reported. Only observational studies are available with many differences in often poorly described patient characteristics, criteria of diagnosis, response to

therapy, and follow-up. Although many cases were treated in general hospitals, complex behavioral problems, probably related to more advanced stages of the disease, often necessitated referral to a psychiatric hospital [6, 15]. Therefore, patient characteristics of those treated in a psychiatric hospital may differ from those treated in a general hospital.

Differences in malarial strains used, number of fever spikes, and pharmacological treatments preceding or following MFT, particularly trypanamide or bismuth, may also have influenced the results [16]. Moreover, detailed evaluation of treatment outcome and differentiation between treatment outcome and spontaneous remission requires a long follow-up period. Factors influencing clinical decision for initiating MFT are rarely noted in the medical records. However, perceived favorable results may have influenced this decision.

MFT-Procedure

The typical MFT practice is described in case A.

No patient aged over 69 received MFT, which is in concordance with MFT practice in Amsterdam [8] and Scotland [6].

Prior to MFT, all patients underwent a detailed examination, since high spikes of malarial fever could be exhausting, especially in conditions like (syphilitic) heart disease, cachexia, diabetes mellitus, obesity, and tuberculosis [5, 6]. Noteworthy, in 8 of 43 cases treated with MFT, an indication of syphilitic aortic heart disease existed. This illustrates that these comorbid diseases were not always considered contraindication. Bed rest, nursing care, and nourishing diet were often applied to improve health status prior to MFT [8]. This may explain why MFT sometimes started more than 2 months after admission.

Disease duration exceeded one year in half of the MFT-treated patients, while in other Dutch hospitals and Scottish asylums, specific therapy was rarely used in patients who had been insane for over a year prior to admission [10, 17]. Due to irreversible tissue damage, complete remission of symptoms was not to be expected in these cases. Nevertheless, partial recovery of neurological and psychiatric symptoms was described [4] and this may explain the application in a rather heterogeneous group of patients.

Patients with all kinds of neuropsychiatric symptoms at admission received MFT, including almost half of the patients with manic symptoms. Studies from this period reported contradictory observations on the relationship between clinical presentation and treatment outcome [4, 6].

Inoculation with malaria was done by patient-to-patient transmission of infected blood, as was the most common method worldwide [3, 6, 7]. In the Netherlands, the malarial species *P. vivax*, Madagascar strain (malaria tertiana), and since 1933 even *P. malariae* (quartan malaria) were most often used [8]. In general, *P. vivax*, due to its supposed benign characteristics, high and regular cycles of fever, and quinine sensitivity, was considered the most suitable species. *P. malariae* was reserved for GPI patients who were not susceptible to *P. vivax* (probably due to immunity acquired by an earlier infection [8]), for those requiring re-inoculation, such as in the above described case B, and for older and more debilitated patients [5].

Complications and Survival

The complications of MFT reported in this study, that is, severe headache, malaise, anaemia, cardiovascular collapse, jaundice, and renal disease, were in part related to the malaria infection. MFT could provoke a daily recurrence of high fevers instead of the aimed recurrence every third or fourth day. In this study, MFT was prematurely terminated in 10 patients, predominantly because of such protracted, daily fevers.

Since no register of diagnosis on admission was available, death statistics was used to identify GPI patients, which may have biased the study to some extent. Patients who improved sufficiently to be discharged could not be included except for those who were readmitted to VvGI and died while hospitalized. Since survival in all GPI patients (MFT- and non-MFT-treated) was longer than in the pre-MFT era, improved medical care may have contributed to prolonged survival. Nevertheless, patients treated with MFT had a significantly longer survival after admission and a prolonged total survival after onset of disease, both 1 year (70 vs. 48%) and 5 years (28 vs. 8%) after admission. This effect of therapy on survival still exists after excluding patients who died within 3 weeks after admission.

It should be kept in mind that on admission, the group of MFT-treated patients was possibly in a better medical condition than the group of non-treated patients and it is likely that this has affected the survival time. However, this is not reflected by differences in baseline conditions that may be associated with higher risk of death (Table 1).

The most important cause of death in MFT and non-MFT-treated patients was progression of the syphilitic disease process, resulting in epileptic seizures, confinement to bed, pressure lesions, and increased risk of pneumonia.

Since only clinical records of deceased patients were examined, the finding of a death rate of 16% within 2 months of MFT could be an overestimation of the actual risks. It has to be emphasized here that several factors contributed to the broad range of reported mortality, such as different criteria for MFT-related mortality, great variation in patient populations, as well as selection criteria for therapy, malarial species, and strains used, number, and height of fever spikes. Nicol, for instance, reported a mortality rate varying from 10 to 15%, depending on the stage of disease and plasmodium strain used [4]. Moreover, MFT-related mortality may have decreased over time due to accumulated experience or increased due to expansion of inclusion criteria as a result of presumed effectiveness [7].

MFT remained the standard therapy for GPI until the discovery of penicillin in the mid-1940s as an effective and safer treatment for syphilis in all stages [6]. However, penicillin therapy was not immediately widely accepted and often applied in combination with MFT to ensure bactericidal antibiotic levels in the central nervous system in the United States and in the Netherlands up to the mid-1960s [1, 5] and in the United Kingdom until the 1970s [5, 6].

Conclusions

MFT was practiced in a wide range of patients with GPI, including those with disease duration of more than 1 year, up to 70 years of age, with a broad array of symptoms and comorbidities, such as (syphilitic) cardiac disease. Notwithstanding these broad inclusion criteria, practice and mortality rates in MFT-treated patients correspond to findings worldwide. MFT was well tolerated and MFT-treated patients had a significantly longer survival. Main causes of death in patients with GPI were epileptic seizures and infectious diseases, irrespective of MFT.

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Disclosure Statement

The authors have no competing interests to declare.

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