Author's response to reviews

Title: A bipolar disorder patient becoming asymptomatic after adjunctive anti-filiarasis treatment: a case report.

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Author's response to reviews: see over
Referee 1

1. What kind of drugs are there for anti-filarial agents? Are they used in other conditions?

The key pharmacological regimens in the management of lymphatic filariasis are diethylcarbamazine, albendazole, and ivermectin either used alone or in combination. Diethylcarbamazine blocks the cyclooxygenase pathway in parasites and leads to death of microfilaria and prevent further adult worm associated lymphatic damage and dysfunction (Fernando et al., 2011). Ivermectin alone can achieve a high microfilaria kill rate and a worm productivity loss with a better response than Diethylcarbamazine. Furthermore, combination therapy seem to have a better macrofilarial effect than monotherapy (Diethylcarbamazine + Albendazole or Ivermectin+ Albendazole)(Fernando et al., 2011).

To the best of our knowledge, these drugs have a broad-spectrum anti-parasitic effect against various nematodes and ectoparasites and have no other indications as psychiatric ones for example.

To complete the case, we added, section conclusion line 3:

“The key pharmacological regimens in the management of lymphatic filariasis are diethylcarbamazine, albendazole, and ivermectin either used alone or in combination. However, combination therapy seems to have a better macrofilarial effect than monotherapy (Fernando et al., 2011).”

2. How was filarial encephalopathy ruled out?

Filarial encephalopathy was excluded because of the absence of abnormal thought processes including confusion, poor memory, and even with weakness and numbness of one side of the body, including facial droop and speech problems. Furthermore, we did not find an incoordination and difficulty walking (ataxia) and finally high Loa microfilaraemia was not found in this case.

To highlight the manuscript according to reviewer’s 1 remark, we added section “case presentation” line 11:

“(absence of confusion, poor memory, incoordination or speech problems)”

Referee 2

1-2 -The introduction comes very briefly on the importance of antimicrobial agents in the treatment of patients with mood disorders. The authors only cite one reference to this subject (Bode L, Dietrich DE, Stoyloff R et al., Amantadine and human Borna disease virus in vitro and in vivo in an infected patient with bipolar depression. Lancet 1997, 349 (9046):178-9). The readers of the manuscript should bare in mind from the introduction of the manuscript, that they are reading about one aspect of the psychiatric management of patients with mood disorders that has been present ever since isoniazid had manifested antidepressant properties.

Authors describe very briefly some of the aspects of filariasis infection such as some epidemiologic data and modes of transmission. It is clear that the introduction of such a case report is not the best place to extensively describe the clinical manifestations of filariasis as well as its diagnosis, treatment modalities etc. but these issues should be generally overviewed and the reader should be oriented to one or two important and recent references in the domain such as: Chandy A, Thakur AS, Singh MP, Manigauha A. A review of neglected tropical diseases: filariasis. Asian Pac J Trop Med. 2011 Jul;4(7):581-6.

We agree with referee 2 that the introduction is incomplete considering, epidemiologic data and other specific treatment for mood disorders. Therefore, we added section Introduction line 3:

“Isoniazid which has been developed for prevention and treatment of tuberculosis, exhibits antidepressant properties. Minocycline, a tetracycline seems to reduce depressive symptoms among bipolar disorder patient (Levine et al., 1996) while clarithromycin, ciprofloxacin, erythromycin and amoxicillin (Lopes et al., 2011; Ahuja et Lloyd, 2007) can lead to a manic episode and therefore are called “antibiomania” (Abouesh et al., 2002). It has
been suggested that mood stabilizing properties of macrolides could act via their interference in the mitochondrial functioning of neurons (Bou Khalil et al., 2012)".

And section Introduction, line 7:
"90% of this infection is caused by W. bancrofti with about 80 countries known to be endemic areas (Chandy et al., 2011). The most important filarial disease for humans is lymphatic filariasis in which the adult worms are present in the lymphatic system (Chandy et al., 2011). Males are more frequently affected (sex ratio 10:1) in their third or 4th decade (Chandy et al., 2011). The incubation period from mosquito bite may be comprised between 4 weeks and more than six months (Chandy et al., 2011)".

3- Authors state that "Usually asymptomatic, rare cases of neurological symptoms have been described" without giving further details. Are those symptoms psychiatric in nature? What do the authors think about the case of acute disseminated encephalomyelitis (ADEM) caused by filariasis described in: Paliwal VK, Goel G, Vema R, Pradhan S, Gupta RK. Acute disseminated encephalomyelitis following filarial infection. J Neurol Neurosurg Psychiatry 2012 Mar;83(3):347-9.

We added some details considering the possible neurologic symptoms of filariasis, section Introduction:
"In monkeys, filarial worms were observed in the bulb, the protuberance, and the cervical cord (Peruzzi, 1928). In humans, several authors described cases with paralysis (Brunètère, 1913), hemiplegia (Tha Mya, 1928, Bertrand-Fontaine et al., 1948), troubles of consciousness (Lukiana et al., 2006). In addition, filariasis is suspected to cause insomnia, mental depression, irritability and severe headaches (Kenney and Hewitt, 1950). A relationship between central nervous symptoms and filariasis appears to be established in these cases, since the surgical removal of adult L.boa, and treatment of the W. bancrofti infections with specific treatment, was followed by the disappearance of symptoms. For to the authors, the neuropsychiatric symptoms observed may be due to the presence of adult worms in vital organs, but the possibility of systemic reactions caused by allergic sensitization of the host to filarial protein has to be considered, regardless of the location of the worms (Kenney and Hewitt, 1950)".

In our case, we do not think that acute disseminated encephalomyelitis could be suspected because the absence of neurologic symptoms as lethargy, irritability, confusion ataxia, seizures, or other signs representing involvement of various areas of the brain and spinal cord. demyelination that predominantly of the white matter of the brain and spinal cord were also absent.

We added section “case presentation”:
"Two weeks after the initiation of anti-filariasis treatment, a successful improvement was observed with clear reduction of agitation and aggressive behaviours that could not be attributed to a modification of psychotropic treatments or filarial encephalopathy or acute disseminated encephalomyelitis (absence of confusion, poor memory, incoordination, speech problems, symptoms of agitation and irritability, confusion ataxia, seizures and demyelination of the white matter). Euthymia was obtained simultaneously with the elimination of the parasite".

4- In the case presentation: Authors mention very briefly that the patient suffers from bipolar disorder. How did they confirm the diagnosis? Is he a patient with a previous psychiatric history of bipolar I disorder or has he been diagnosed of suffering from the disorder because of the actual episode? In case the patient had already been diagnosed with bipolar type I disorder, what are the features of this diagnosis (how many years elapsed since the onset of disease? how many hospitalizations? what drugs have been given in the past? is there a history of substance abuse?)

The diagnosis of bipolar disorder was confirmed according to DSM-IV criteria

We added section case presentation “(DSM-IV criteria)"
"The patient had a previous psychiatric history of depression and delusions 3 years before but the diagnosis of bipolar disorder was not evoked. It was the third relapse for the patient and two previous hospitalizations have been conducted in Congo. The patient was treated by haloperdidol before. There was no history of substance abuse".

5- In the case presentation: Authors mention briefly that the patient suffered from a manic episode with agitation and aggressive behavior and that he received benzodiazepines, FGAs, SGAs and mood
stabilizers with no efficacy. Could the authors be more specific regarding the current clinical presentation of the patient? What were his symptoms? Was he delusional or not? How many weeks has he been manifesting manic symptoms before his admission? How much did he score on the Young Mania Rating Scale (YMRS) at his admission? What are the names of the psychopharmacologic drugs he received? at what dosages and for how long? What clinical and paraclinical tests have been done on admission? Were they all normal except for the hypereosinophilia? Was it possible to make a complete neurologic examination to him? Was he compliant to his pharmacologic treatment?

The patient was agitated, aggressive, presented a logorrhea, an hyperactivity with irritability, insomnia, perseverative and mystic delusions. The manic symptoms began about one six weeks before the admission. The YMRS score at admission was 43.

The patient received clonazepam (8mg) for several weeks with loxapine (400mg) then cyamemazine (400mg) and aripiprazole (25mg) then olanzapine for two weeks. Amisulpride was conducted at 1200mg/per day for several weeks. Finally, salt valproate was administrated at 1250mg/per day for several weeks.

Neurological and somatic examination of the patient was normal. Paraclinal tests including routine blood and urine examination were normal excepted an hypereosinophilia. The MRI of brain was normal.

The patient was compliant for treatment.

Therefore, we added in the manuscript section “case presentation”:

“The patient had a previous psychiatric history of depression and delusions 3 years before but the diagnosis of bipolar disorder was not evoked. It was the third relapse for the patient and two previous hospitalizations have been conducted in Congo. The patient was treated by haloperdidol before. There was no history of substance abuse. Native of Congo, he was admitted in a psychiatric ward for a manic episode with agitation, irritability, logorrhea, aggressive behaviour and delusions (persecutive, mystic and megalomaniac)(YMRS=43). The excitement and insomnia escalate to become dangerous, including physical violence needing physical restraint and seclusion. Pharmacological agents used to treat agitation including benzodiazepines, first- and second-generation antipsychotic drugs, and mood stabilizers showed no efficacy in spite a good compliance. The patient received clonazepam (8mg) for several weeks with loxapine (400mg) then cyamemazine (400mg/day) and aripiprazole (25mg) then olanzapine. Amisulpride was conducted at 1200mg/ per day for several weeks. Finally, salt valproate was administrated at 1250mg/per day for several weeks. Neurological and somatic examination of the patient was normal. Paraclinal tests including routine blood and urine examination were normal excepted an hypereosinophilia. The MRI of brain was normal”.

6- In the case presentation: regarding the discovery of filariasis, has any test been done in order to eliminate an ADEM or any other neurologic impairment due to filariasis? Did the patient accept to take the antihelmintics without resistance? What was his YMRS estimated at after two weeks of administration of antihelmintics? Have any psychopharmacologic drug been introduced or escalated in dosage during the administration of antihelmintics?

An ADEM or neurologic impairment was not suspected because of the absence of neurologic symptoms and MRI abnormalities.

The patient accepted to take antihelmintics and no drug was introduced or escalated in dosage during the administration of antihelmintics. YMRS score after 2 weeks of antihelmintics drugs was of 9.

We added section case presentation "(YMRS=9)"

7- In the conclusion section: It is not clear whether the final hypothesis of the authors is in favor of a certain antimanic effect of albendazole or ivermectin or that they think that an infectious state might interfere with the efficacy of mood stabilizers. As a matter of fact, authors are making some assumptions throughout the manuscript that are not clearly formulated in the conclusion section. The improvement of manic symptoms in their patient could be related, in my opinion, to four possible explanations that should better be further discussed:

a- Antihelmintics, especially ivermectin which is a semisynthetic macrolide, may have mood stabilizing properties. Authors can refer to: Bou Khalil R. Is there any place for macrolides in mood disorders? Med Hypotheses. 2012 Jan;78(1):86-7.
We agree with reviewer’s 2 remark that ivermectin may have mood stabilizing properties and can explain our case.

We added section conclusion: “One explanation could be given by the fact that ivermectin which is a semisynthetic macrolide, may have mood stabilizing properties via their interference in the mitochondrial functioning of neurons (Bou Khalil et al., 2012”).

b- The patient is presenting a manic episode that is no more than the manifestation of an ADEM (unless the authors gave the sufficient proofs that it is not an ADEM or any neurologic manifestation related to filariasis). In the case where an ADEM is probable some references regarding neuropsychiatric manifestation of ADEM must be included such as: I- Krishnakumar P, Jayakrishnan MP, Devarajan E. Acute disseminated encephalomyelitis presenting as depressive episode. Indian J Psychiatry. 2011 Oct;53(4):367-9; IIPatel SP, Friedman RS. Neuropsychiatric features of acute disseminated encephalomyelitis: a review. J Neuropsychiatry Clin Neurosci. 1997 Fall;9(4):534-40.

We agree that we have to take into account this hypothesis. However, in the absence of clinical symptoms and brain imaging abnormalities, it is difficult to retain this hypothesis.

We added section conclusion “Filariasal and acute disseminated encephalomyelitis should be evoked in such cases. However, the absence of neurologic symptoms and brain imaging abnormalities led us to not retain this hypothesis”.

c- The comorbid infection with filariasis provoked a resistance of mania because of an inflammatory state exacerbated by the parasitic infection in a way that cytokines were influencing the CNS and mood stabilizers became inefficient. In this case authors have to present more data about what kind of cytokines are dysregulated during filariasis infection and what is the known effect of these cytokines on mood?

See question 1, referee 3.

d- The treatment with antihelmintic was a fortuitous association to the recovery from the manic episode due to causes unrelated to the parasitic infection.

We agree with reviewer’s 2 remark and added section conclusion:

“However, it is often difficult to determine whether changes in the levels of cytokines are the result of the medication’s pharmacological properties or whether they are reflecting changes in the clinical status of the treated patient. Therefore, the spectacular improvement after introducing antihelmintics can be attributable to the natural course of the manic episode and not to the introduction of antihelmintics”.

8- In the conclusion section: Authors are concluding that antiparasitic drugs "could be useful as they are known to have immuno-modulatory properties (4) especially among patients native from endemic countries”. It is not clear what the authors mean by this sentence because antiparasitic agents have immuno-modulatory properties not only in patients native from endemic countries.

We agree with reviewer 2 that this sentence is not clear. Therefore, we added section conclusion: “especially among patients native and those living or travelling in endemic countries”.

Minor essential revisions:

9- Some sentences in the abstract especially the sentence constituting the conclusion might need some restructuring after modifying the text body.

We modified the abstract according to the several modifications in the text body.

10- More keywords such as "mood stabilizers" should better be added.
We added the keyword “cytokines, mood stabilizers”

Referee 3

Major Compulsory Revisions:

1. Authors discussed only shortly the mechanisms of immunopathological reactions that might play manic-induction role. Some details (cytokines?) should be provided for manic episode induction, which decrease due to the albendazole action might take part in symptoms decrease. It was described earlier the possibility of neuropsychiatric aspects of filariasis e.g. L. Van Bogaert, A et al. ENCEPHALITIS IN LOA-LOA FILARIAISIS. Neurol Neurosurg Psychiatry. 1955 May; 18(2): 103–119. or G Dreyer, D Mattos. Lymphoedema and delusional parasitosis - Journal of Lymphoedema, 2008.

We agree with referee 3 and 2 that the immune dysbalance succeeding a filarial infection and the potential role of albendazole is missing.

We added, section introduction “A post mortem study of filarial encephalitis showed a diffuse inflammation of the white matter (in a less extent, the grey matter), perivascular inflammation and a dramatic allergic reaction explaining serious neurologic symptoms (Van Bogaert et al., 1955)”. Furthermore, it is possible that albendazole improved the manic episode using an immunological pathway. Indeed, it has been demonstrated that repeated albendazole treatment cause significant increases in production of the Th2 cytokines IL-5 and IL-13, by peripheral blood leukocytes (Cooper et al., 2008). It is well known that Th1 system is overstimulated among manic patients leading to a production of proinflammatory cytokines.

We added section conclusion: “It is has been demonstrated that repeated albendazole treatment cause significant increases in production of the Th2 cytokines IL-5 and IL-13, by peripheral blood leukocytes (Cooper et al., 2008). It is well known that Th1 system is overstimulated among manic patients leading to a production of proinflammatory cytokines (for review, see Hamdani et al., 2012). The effect of albendazole on Th2 cytokines can inhibit the Th1 system leading to an anti-inflammatory responses and a downregulate of the systemic inflammation. Therefore, filariasis by inducing chronic inflammation and immunopathologic reactions seems to play a major role in infected affective disorders by changing levels of cytokines of the Th1 system (IFN-gamma, TNF-alpha, GM-CSF, IL-1alpha, and IL-8)(Babu et Nitman, 2003) or indirectly damaging the brain tissue via an immunological pathway. Mood stabilizers are known to downregulate neuroinflammation and excitotoxicity and may have exerted in our case a joint effect with antihelmintics.”

Minor Essential Revisions:

1. Each abbreviation should be defined when used for the first time in the manuscript e.g. BDV.

We added (Borna Disease Virus) in the section Introduction

2. Manic episode should be more detailed described e.g. how long lasted?

For the answer, see referee 2, question 4&5

3. Acting substance should not be written in capital letters.

We corrected this error

4. Authors mentioned that “The fortuitous discovery of a hypereosinophilia led to the diagnosis of a filariasis bancrofti infection” but by which method was diagnosed? I believe that not only based on the hypereosinophilia.

Referee 3 is right; filariasis infection was diagnosed in the laboratory of parasitology using an immunodiagnostic method.
Therefore we added, section case presentation: “The fortuitous discovery of a hypereosinophilia led to the diagnosis of a filariasis bancrofti infection using an immunodiagnostic method”

5. Authors mentioned that “...agitation and aggressive behaviours that could not be attributed to a modification of psychotropic treatments” but which modification of what?
By could not be attributed to a modification of psychotropic treatments, we mean no modifications of the dosage of treatments.
We added, section case presentation “that could not be attributed to a modification of psychotropic treatments (modification of dosages)”

6. Were any physical symptoms of filariasis?
There were no filariasis symptoms, we therefore added section case presentation: “We did not find filarial symptoms in our patient”

Referee 4

Minor Essential Revisions

1. What was the actual basis for the diagnosis bancrofti filariasis infection -
Filariasis can't be diagnosed based only on hypereosinophilia.
The diagnosis of filariasis infection was done using an immunodiagnostic method (see question 4, referee 3).

2. What were the reasons for the diagnosis of bipolar disorder (DSM-IV)?
See question 4&5 of referee 2

3. Please convince me that:
a. antiparasitic treatment removed the cause of the disease and not just the symptoms - side effects (neurotoxicity);

We took in charge this patient in our unit with major difficulties: major agitation, aggressive behaviour, inefficacy of treatments for several weeks. We don’t think that treatment were not tolerate because of the absence of neurologic symptoms such as confusion. We were surprised that anthelmintics treatments when joint with usual treatment led to an improvement of the disease. Our hypothesis is that filariasis caused a dysbalance of the immune system (which can be found in manic episode) leading to the overproduction of cytokines known to be neurotoxic for the brain. Anthelmintics, as albendazole, can restaure this dysbalance and therefore attenuate the inflammation. However, it remains a hypothesis as the dosage of cytokines was not done in this case. We think that psychiatrics could bare in mind that refractory patients to usual treatments need further somatic investigation as infections.

b. antiparasitic treatment was successful - are there any diagnostic test results, which confirm the eradication of filariasis?
We controlled the immunoserological status of filariasis among this patient 3 and 4 months after the initiation of anthelmintics and found an eradication of the parasite.
To complete the manuscript, we added, section case presentation “Euthymia was obtained simultaneously with the elimination of the parasite (according to immunodiagnosis status)”.

4. How could you explain the joint effect of antihelmintics with mood stabilizers? authors’ explanation is very enigmatic.
See question 1, referee 3.

Discretionary Revisions

1. It is better to avoid abbreviations in the text - please explain what BDV means.
We added (*Borna Disease Virus*) in the section Introduction.

2. BMC Psychiatry journal is widely known and available around the world, so it must be a comprehensive journal - indicate that similar symptoms can also affect tourists who stayed in endemic areas.

We added section conclusion:

"especially among patients native and those living or travelling in endemic countries".

Additional references


