

Glioblastoma multiforme – Standard therapy and apitherapy

Apitherapy clinical breakthrough

Case no.19 – male / 40 years old / 1.68 m/ 126 kg

Abstract

We are presenting the clinical case of a young man, who was diagnosed with glioblastoma multiforme (GBM) at the age of 35.5. Having had initial surgery for a primary tumour, undergoing a second surgery following relapse and having then undertaken both chemo and radio-therapy in the neurosurgery departments of two university hospitals in Germany, he turned to Apitherapy Medical Center in Romania to undergo Apitherapy following his second relapse.

He resorted to Apitherapy after his Karnofsky Performance Score (KPS) had dropped significantly over a very short period of time, following his second surgery (caused by his first relapse) – from KPS 100 to KPS 50, due to a new, more aggressive relapse. At that stage, the patient's family were informed that the clinics had no efficient antineoplastic treatments left to use at such an advanced stage in tumour progression. The family brought the patient back to Romania where he commenced an apitherapy treatment. After two and a half months of apitherapy, the patient had to return to Germany every month: it was both an insurance-related issue and a curiosity shown by the clinical experts towards the efficiency of other methods and other therapy agents used, as well as a degree of surprise regarding the patient's evolution – a patient who had been given no chances of survival. Discharged from hospital with a KPS score of 50, the patient went through an assessment after three and a half months of apitherapy, when his clinical state was evaluated at KPS 60. After another month, his KPS score was assessed at 70.

This evolution became constant during his apitherapy treatment. Every time the patient went through an MRI scan in Germany –on native tissue and with contrast agents – the results showed a clear retreat of the tumour invasiveness specific to the mitotic aggressiveness of GBM. At the same time, the patient went from cognitive absence and suffering, to becoming a normally oriented person from a cognitive viewpoint, without any sensorimotor deficiencies. All these effects were attributed to the little known cytostatic potential of apitherapy substances, which had blocked the mitosis process thus forcing the tumour into remission. Additionally, from a synergy viewpoint, the apitherapy substances also prohibited the neo-angiogenesis process and they restrained the functionality of previously existing neofunctional micro-blood vessels.

We are convinced that, if GBM were approached as a succession of multiple dysproteinaemias, where the autoimmune dysproteinaemia precedes the immunosuppressive dysproteinaemia, the illness' prophylaxis would be possible in its autoimmune stage. In cases of primary intra-skull tumours, we think that apitherapy should be applied before the first surgery, due to its anti-angiogenesis and its cytostatic potential.

The evolution of our young patient proves something that neither fundamental medical research nor clinical research should ignore: the very little known but nonetheless huge immunomodulatory and tumour-fighting potential of scientific apitherapy. This would be in the patients' best interest¹.

A general overview of Glioblastoma multiforme

Glioblastomas are a type of brain tumour and the most frequently encountered intra-skull cancers² in the world: they make up for approximately 15% of total intra-skull cancers and 50% of glial

¹This study is based on medical documents issued by German clinics and labs and by Romanian medical labs. We are happy to make them available to any researcher or doctor interested in visiting us. We obtained the family's consent to use them and we protected the patient's identity. The documents are stored in our database, under reference: **R20/112 - B6, Apitherapy Medical Center database**

²The simplest classification of intra-skull tumours - which is also consistent with our practice of regarding them as dysproteinaemias - is done based on the cells they grew from: glial tumours (made of glial cells) meningeal tumours

tumours. About 60% of gliomas are highly malignant and they become glioblastomas (GBM). Their evolution prognosis is generally quick and very reserved. GBM can affect patients of all ages – such as the 35 year old patient we are discussing now – but it is more frequently encountered after the age of 55, with a peak in the number of cases between 65 and 74³. Its causes are little known, with some cases (the lowest number – about 5%⁴) being deemed as genetic⁵, although this theory is insufficiently supported by evidence. When talking about GBM causes, we are actually talking about *risk factors*: exposure to ionizing radiation, mobile phone radiation, electromagnetic fields (high voltage power lines), certain sweeteners (aspartame), pesticides, synthetic rubber, formaldehydes, etc. Other risk factors are associated with autoimmune diseases, asthma, neurofibromatosis, Li Fraumeni Syndrome (which is genetic, with a dominant autosomal transmission) etc. ***Among the various, sometimes contradictory classifications of glioblastomas***, the most commonly used is the one provided by WHO, according to which, out of the 4 established levels (Kernohan):

- level 1 glioblastomas are benign: when they are neuro-investigated *they show no mass effects*.
- level 2 glioblastomas are less aggressive, they are mostly encountered in young patients and they have a lower malignancy level, with a survival period of up to 8 years. *When they are neuro-investigated, they show mass effects, but no contrast plug*.
- level 3 glioblastomas: bearing atypical nuclear aspects and atypical mitoses, they are more aggressive and have a more reserved prognosis. *When they are neuro-investigated, they show contrast plug*.
- level 4 glioblastomas: are mostly encountered in elderly patients, they *show a high invasiveness degree* and pleomorphism. From a nuclear viewpoint, they show an increased mitotic activity, necrosis areas and endothelial hyperplasia; despite all complex treatments, their survival rate is extremely low. ***Glioblastoma diagnosis*** is based on imaging: CT scan (computerised tomography) and/or MRI scan (Magnetic Resonance Imaging). MRI scanning, on native tissue or/and with contrast agents, provides more details than CT scanning. Diagnostic imaging is generally resorted to only when the doctor recommends it to the patient, based on suggestive symptoms: headaches, vomiting, loss of appetite, weakness, chronic fatigue, sight disorders, papillary oedema, skull nerve paresis, cognitive and behaviour alterations, sensorimotor deficiencies, epilepsy, etc. Some intra-skull tumours can even be discovered by accident, during investigations conducted for other suspected diseases. The MRI can also direct the surgeon, during surgery, thus helping him/her avoid hurting certain areas that are important for memory, speech, locomotion, etc. Level 4 GBM (like the one our patient suffers from) show on medical imaging devices as irregularly shaped, barely delimited, hypodense tumour masses, bearing areas of tumour necrosis, surrounded by peripheral

(made of meninges cell), neural tumours (having their initial point in the nervous cells) schwannomas (made of the nervous sheath cells)

³The fact that glioblastomas kick in, mostly, after the age of 55 might be consistent with our theory on the debut of intra-skull tumours, which are regarded as a succession of dysproteinaemias, going from autoimmunity to immunosuppression. During the precursor stage, which is the auto-immune stage, there are local (and detectable) accumulations of spongioblastoma origin, leading to the formation of benign gliomas. If somebody compared, through TP and SPE, the evolution of blood proteins, during the benign stage – the glioma stage – they would discover values comparable to the ones discovered, for instance, during the formation of uterus fibromas (hypoalbuminemia and hyperglobulinemia – with a more serious increase of immunoglobulin γ -, accompanied by ionic hypocalcaemia). We shall keep in mind the fact that, during the formation of benign fibrosis, hypoalbuminemia is accompanied by ionic hypocalcaemia. If gliomas can be discovered not only in elderly but also in younger patients and, sometimes even in children, this is due to a shared evolution of blood proteins and calcium concentrations, common to autoimmune fibrosis diseases. We have mentioned congenital autoimmunity before, either caused by a congenital predisposition or gained, a disease that is pathological in children, youngsters and the elderly alike. However, the elderly person's autoimmunity is a physiological (normal) state. This does not mean that "age related" auto-immunity has no pathogenic effects, it only means that such auto-immunity is normal, inevitable and progressive at certain ages, given the fact that the liver's ability to synthesise albumin, decreases with age while the synthesis of fibrotic globulin proteins, grows.

⁴Genetic breast cancers record approximately the same percentages: 3-5%.

⁵ Mutations of the p53 tumour suppressor gene are particularly incriminated - the loss of this gene's expression leads to uncontrollable cellular multiplications. This kind of mutation shows in other types of cancer as well. Other gene mutations are also taken into discussion.

zones of increased cellularity and infiltrated by neoformation blood vessels. The oedema shows in peritumoral areas and it can be more or less important. This type of tumour bears a high degree of invasiveness and it can affect, at first, one single frontal lobe, then both frontal lobes (“butterfly” glioma), then both parietal lobes, then the brainstem, being able to thalamically disseminate into the cerebrospinal liquid (LCR) but being very rarely able to disseminate systemically.

Standard glioblastoma therapy implies:

- *surgical intervention* in order to resect and remove the tumour, to the extent possible. Surgery is always followed by a microscopic examination, for accurate diagnosis; complete surgical cytoreduction is practically impossible, due to the blurry delimitation of the tumour, from its surrounding cerebral tissue.

- *cytostatic chemotherapy*

- *radiotherapy*: it is used both in case of inoperable tumours and after surgery, associated with chemotherapy.

- *adjuvant medication, associated with chemo and radiotherapy*: it can be prescribed based on the symptoms or to restore certain unbalances: anticonvulsant, anticoagulant, anti-oedematous, antiangiogenic, antiemetic, etc.

Patients’ evolution after chemo and radiotherapy is usually assessed in accordance with the Karnofsky Performance Score (KPS). We shall not present here, the entire KPS “scale” which ranges from 100 (a good state of the operated and chemo-treated patient, with no signs and symptoms of illness) to 0 (exit). We shall only present the features of those Karnofsky scores that are related to our patient. They shall be taken exactly as they were written in the medical assessment bulletins issued by the two German university clinics and even their chronological order shall be kept. There will be, however, an exception: the October 2010 assessment, when the family brought the patient to Apitherapy Medical Center - this assessment being the only one that belongs to us.

Evolution of the Karnofsky Performance Score during standard therapy:

- Karnofsky Score - 100%: the patient is in a normal state, without any symptoms or signs of disease (**July 2010**, after the second surgery conducted for the first relapse)

- Karnofsky Score - 50%: The patient needs considerable assistance and frequent medical care (**September 2010** when doctors decided that no antineoplastic therapy could be efficient anymore).

- Karnofsky Score –40%: *The patient is disabled; he needs specialised assistance and care* (**October 2010**, when the patient resorted to apitherapy¹).

Evolution of the Karnofsky Performance Score during apitherapy:

- Karnofsky Score – 60%: The patient needs occasional help but he can generally take care of his own personal needs (**January 2011**, after three and a half months of apitherapy)

- Karnofsky Score – 70%: The Patient can take care of himself but he cannot conduct normal activity or fulfil an active work (**February 2011**, after four and a half months of apitherapy); this level was maintained until **April 2012**, when an MRI scan conducted in Germany showed the glioblastoma had resumed its progression.

We anticipate the comparative presentation of the patient’s clinical evolution, using KPS as sole indicator, with the declared intention to increase interest towards the following evolutions:

- *during standard therapy* – after the second surgery, KPS dropped from 100% to 50% in two and a half months (July-September 2010)

- *during apitherapy*, KPS went up from 40% to 60% in three and a half months (October 2010-January 2011); during the next month – February 2011 – KPS grew to 70% and it stayed at this level for one year and two months (February 2011-April 2012).

We regard this positive evolution recorded between October 2010 and April 2012, due exclusively to apitherapy, as a unique case of tumour remission from KPS 40% to KPS 70%, while

¹ It is the only KPS assessment that belongs to us. It corresponds to the patient’s clinical state at the time he took up apitherapy.

such a long steadiness at KPS 70% was completely unusual. This success was due not only to the incomparable tumour-fighting efficiency of apitherapy substances but also to the method used - which was to approach the glioblastoma as a dysproteinaemia.

Glioblastoma treated as a dysproteinaemia

We deemed intra-skull cancers as being the result of two types of successive dysproteinaemias, autoimmune and immunosuppressant: *The precursor autoimmune dysproteinaemia*, characterised by hypoalbuminemia and hyperglobulinemia (with an increase of globulin γ (*immunoglobulin*) over the upper limit of normal value range - n.v.), associated with ionic hypocalcaemia and, often with hyperlipidemia; *benign gliomas grow during this stage.*

- *dysproteinaemia, marked by immunosuppression*, characterised by percentage hypoalbuminemia, hyperglobulinemia, especially at γ level, associated, in all cases, with an increase of Ca^{2+} and constantly with hyperlipidemia and hyperglycaemia. The cancerization process takes place during this stage: *the glioma becomes a glioblastoma.*

No matter what the causes or the favouring factors of glioblastoma formation might be, the autoimmune stage – with its spongioblast proliferation – is a *sine qua non* condition, regardless of the **causes for the autoimmune dysproteinaemia:**

- *congenital inheritance of maternal dysproteinaemia*¹, passed on from mother to foetus – marked by hypoalbuminemia and hyperglobulinemia, accompanied by ionic hypocalcaemia.
- *gaining a protein status specific to autoimmune diseases* - hypoalbuminemia and hyperglobulinemia, associated with ionic hypocalcaemia:
- through a diet too rich in proteins², with aliments containing excessive amounts of amino acids that are precursors of globulin proteins and not enough amino acids that are precursors of albumin.
- through a diet too rich in lipids: leads to a percentage reduction of albumin, through the effects it has on hepatocytes.
- alcohol abuse – can lead to hypoalbuminemia
- going through infections that have inflammatory effects – bacterial, viral, etc – which stimulate the increase of globulin γ , evolving towards autoimmunity.
- as a iatrogenic effect of certain medications, etc.

Intra-skull cancers are diseases caused by chronic dysproteinaemia, associated with the corresponding evolution of the immune system functions. The proliferation of fibrous proteins and the tissue disorganisation under autoimmunity conditions can also be encountered in cases of other diseases with fibrosis effects and in cases of other types of cancers that are preceded by fibrosis processes. The autoimmune benign glio-fibroma, which was initially formed, later turns malignant and it becomes a glioblastoma. The cancerization process is marked by a transition from autoimmunity to immunosuppression – globulin γ drops towards – especially below the minimum limit of n.v., which leads to the percentage increase of albumin (ALB), a fact underlined through serum proteins electrophoresis (SPE). The symptoms of benign glio-fibromas (if there are any) are

¹Maternal dysproteinaemia marked by hypoalbuminemia and accompanied by hypocalcaemia can determine the congenital autoimmunity of a new-born. The foetus grows using substances from the mother's blood. Besides, when organogenesis reaches a certain stage, the foetus itself takes part in the production on proteins. However, its body cannot use (for its proteinogenic functions) other proteins than the ones existing in the placental blood, and placental blood is maternal blood. Thus, the mother's protein status - dysproteinaemia with hypoalbuminemia- is taken over by the foetus, associated with hypocalcaemia. This explains why some children develop autoimmune diseases ever since their first months or years of living – such as asthma, uveitis, fibrinoplastic, juvenile arthritis, etc – which are generally deemed to have idiopathic causes in the clinical literature. Nothing could be less accurate. If many of the diseases affecting new-borns were regarded as dysproteinaemias passed on from the mother to the foetus, we would not have now such a long list of illnesses whose causes are deemed as unknown (idiopathic, cryptogenic). If TP, SPE, CaT and Ca^{2+} tests were done both to the mother and the child, the autoimmune dysproteinaemia and the ionic hypocalcaemia common to both of them, could be easily noticed.

² Just like intra-skull cancers, autoimmune diseases are more frequently encountered in rich countries, where there is an excess of food rich in a protein, lipid and glucid substances, whereas in poor countries, illnesses caused by infections and malnutrition prevail. We assume that this discovery – which does not belong to us - confirms, at least indirectly, our theory on the autoimmunity – intra-skull cancer succession.

reduced to the symptoms determined by any eventual pressure applied on the brain, in the formation surrounding area. Gradually, as the cancerization process takes place, other symptoms start showing in a relatively short period of time and their number and intensity are increasing constantly. The occurrence of these symptoms is generally the marking point indicating the start of medical investigations for diagnostic purposes. There is a certain period of time between the start of cancerization and the beginning of invasiveness that turns the tumour into a glioblastoma multiforme. Due to the rapid mitosis specific to glioblastomas, the probable length of this period is much shorter than the autoimmune accumulation stage, needed for the formation of glio-fibroma.

At least two questions can be asked with regards to these three stages - glioma formation, cancerization and beginning of invasiveness:

- *During which of the first two stages does the vascularisation¹ of glio-fibroma occur?*
- *If prophylaxis is possible, during which of the first two stages would it be beneficial?*

Medical literature states clearly that there is no prophylaxis therapy for GBM. In most cases, these tumours are diagnosed only after they become malignant. The question, however, still stands: *could a prophylaxis therapy be initiated for glioblastomas?* We think it could, but only when total proteins (TP), serum proteins (SP), total calcium (CaT) and ionic calcium (Ca^{2+}) become routine lab tests, determined through SPE, while lipidemia and glycaemia are regularly assessed (hyperlipidemia and hyperglycaemia are constantly associated with these tumours).

When fibrosis processes are suspected – due to hypoalbuminemia, hyperglobulinemia and ionic hypocalcaemia – an MRI scan could show a benign glioma (of small sizes, confined to one location, without neovascularisation, non-invasive, without oedema) even in the absence of other suggestive symptoms. At this stage, balancing the TP level by balancing SP – which is indicated through SPE – as well as by restoring the physiological limits of Ca^{2+} , of lipidemia and glycaemia, can prohibit the glioma from continuing its autoimmune growth process, it can prohibit the neoangiogenesis² process, or it can stop it if the process is already ongoing, it can prevent the occurrence of oedema. Under such conditions, the glioma might resorb itself, it might stay benign or it could be completely eradicated through surgery. Anyway, there is real chance of intra-skull tumour prophylaxis by keeping proteinemia, calcaemia, lipidemia and glycaemia within normal physiological limits, or by restoring their unbalances in good time, as the case may be.

Therefore, from a para-clinical viewpoint, summarising the evolution of proteinemia:

¹Neovascularisation in glioblastomas, which helps feed the tumour and facilitates invasiveness, has certain particularities. We shall not discuss them here. The medical literature states that neovascularisation begins when the balance between angiogenic and anti angiogenic factors deteriorates in favour of the first category. No role is granted to albumin in controlling the formation of neo-blood vessels. There is a permanent inter-conditioning process between albumin and globulins, an inter-regulation process within TP. Hepatic hemangiomas for instance, occur in conditions of hypoalbuminemia. The vascularisation of breast fibroadenomas also occurs against the backdrop of a continuous albumin drop, but only after they had already become cancerous. In case of uterus fibromas, neovascularisation precedes the beginning of fibroma formation, but they very rarely become cancerous. We should know when the neovascularisation of gliomas is initiated: before their formation, as in the case of uterus fibroma or after the already formed gliomas become cancerous, as in the case of breast fibroadenomas that go through cancerization. The fact that certain gliomas comprise a pre-existing blood vessel which “transits” the glial “conglomeration” from the start, cannot be taken as glioma neovascularisation.

²The low level of albumin favours neovascularisation. The number of anti-angiogenic medicines is constantly growing but the clinical cases reported, describing their effects are not very encouraging. This is not the place to list angiogenic or anti-angiogenic factors, nor is it the place to list medicines with intended anti-angiogenic effects. In our experience, by restoring the A/G balance, we obtain the resorption of neo-blood vessels infiltrating cancerous breast fibroadenomas – provided that each globulin was within normal values – and thus, these tumours could be removed by surgery, without any risk of metastasis. The imaging material accumulated in our database proves the anti-angiogenic potential of apitherapy substances in uterus fibromas as well. From an apitherapy viewpoint, by rebalancing TP, depending on the SPE values, you can obtain more than through classic embolization. By fully resorbing the neo-blood vessels or by reducing the functionality of their lumen, fibromas were either resorbed or they stopped growing. (Code: R5/64-B2; R5/66-B7; R9/89-B13; R9/162-B16- Apitherapy Medical Center Database). In the present case, we attribute the prohibition of GBM progression for such a long period of time (October 2010 – April 2012) to the anti-angiogenic potential of apitherapy substances.

- **Autoimmune diseases show:** - hypoalbuminemia
 - hyperglobulinemia (globulin γ and IgG are the ones increasing most often)
 - ionic hypocalcaemia (regardless of the CaT level)
- **Intra-skull cancers show:** - percentage increase of ALB, towards the upper limit of n.v.
 - globulin γ and IgG record minus values, especially below n.v.
 - Ca^{2+} is always showing normal values, no matter what the CaT level is.
- **In case of other cancers we notice:** - hypoalbuminemia;
 - hyperglobulinemia (specially at γ level);
 - Ca^{2+} within normal range.

Standard therapy for Glioblastoma (Germany: January 2006 – September 2010)

Until he took up apitherapy, the patient had undergone two surgeries – with the involvement of two University Clinics in Germany and a medical practice specialised in radiology and nuclear medicine, also in Germany. The first surgery was conducted for the glioblastoma whilst the second was conducted for a tumour relapse, and each time the standard therapy protocol for such intra-skull tumours was followed: chemotherapy and radiotherapy, associated with adjuvant antibiotics, anticonvulsants, anticoagulants, antiemetics and steroid inflammatory medicines (with immunosuppressant role). What's exceptional is the fact that, three and a half years had passed between the first surgery - conducted for the resection of the primary tumour – and the second surgery – conducted for the first relapse. This period of time (which is relatively long for such cases) was due to the doctors' professionalism and the patient's young age. However, when the patient resorted to apitherapy, he had run out of other options, since there were no efficient antineoplastic treatments left to try, a fact that had been communicated to the family.

We shall resort to chronology to make the patient's evolution easier to track and we will use the medical documents received from Germany:

- **Winter 2005** – age 34.5, the patient started experiencing forehead pains, whose intensity and frequency gradually increased.
- **January 2006** – age 35.5, the patient **went through surgery for** left frontal lobe **glioblastoma**, which was diagnosed, from a histopathological viewpoint, as glioblastoma multiforme, a level IV glioblastoma by WHO standards:
 - cytostatic chemotherapy was done next, with Temodal – 12 cycles
 - February - April 2006 – the patient went through radiotherapy (totalling 61.2 Gy)
- **May 2009** – three years and three months after the first surgery, an MRI investigation revealed both **a tumour relapse and a tumour invasion to the right frontal lobe**;
- **June 2009** - the patient went through a second surgery: **the relapsed tumour was resected**.
 - he went through intensive cytostatic chemotherapy with Temodal.
 - he went through radiotherapy (totalling another 50 Gy).
- **July 2010, when the patient returned to the clinic for a reassessment:**
 - he stated to tolerate chemotherapy well, although, lately, he was experiencing fatigue and apathy states more and more frequently.
 - the doctors deemed him as being cooperative, well oriented and without any sensorimotor deficiency.

Recommendations: - to carry on radiotherapy with one week breaks

- to be administered AIS depending on the cytostatic treatment's effect on the blood;
- to return to the clinic for a new consultation after 4 weeks;
- the patient's clinical state corresponded to a **Karnofsky Score of 100%**
- **September 2010 – a new clinical assessment revealed:**
 - significant tumour progression;
 - serious deterioration of the clinical state
 - the patient's clinical state now corresponded to a **Karnofsky Score of 50%**
 - **the absence of any therapeutic option¹** was discussed with the family;

¹ „In Zusammenschau aller Befunde sehen wir keine Therapieoption mehr.“

- the patient was sent to a different Neurology university clinic for another assessment.
- **September 2010: after examining the patient, the other university clinic informs the family that:**
 - the tumour had resumed its bi-frontal growth, now also invading the ventricular system
 - a new tumour resection became useless (given its spread).
 - chemotherapy could not be carried on either (it had already been done intensively)
 - radiotherapy could not be carried on either (the patient had already accumulated over 110 Gy)
- **The patient's clinical state was so deteriorated that no antineoplastic therapy² could be efficient any longer, fact which was communicated to the family.**
- no date was set for the patient to return for reassessment (which was relevant for the prognosis given to the patient's evolution);
- the family could call the clinic any time, when the patient's state became so poor that he would need permanent medical attention;
- In ambulatory, the family was advised to administer Avastin³ to the patient (he did not tolerate it and his clinical state continued to worsen). In the second half of September 2010, the patient's family turned to apitherapy as a last resort. For this purpose, the patient is brought to Romania together with his mother, who looked after him.

Glioblastoma apitherapy (Romania: October 2010 – July 2011)

When he took up apitherapy, in October 2nd 2010, the patient was almost 40 years old. He was obese, weighting 126 kg at a height of 1.68 m. He was suffering from incontinence and was wearing nappies. His vocabulary was limited to very few words (the most usual ones) which were not pronounced very clearly: *no, yes, give me, I want, I don't want*. He could no longer read or write. He no longer remembered that he had been married and he had a little boy. He only recognised and communicated with his parents, who were looking after him. He answered no questions and he showed no interest in any person he came in contact with. He was only interested in watching TV, but only to watch cartoons. He had difficulties walking, going wherever he was guided, just like a mechanical toy, with no conscious intention of getting anywhere for any purpose. While he was sitting on a chair, in the medical assessment room, his head kept falling every now and then towards his left shoulder and he kept falling asleep "instantly", but only for one or two minutes. At some point he sat on the floor, he got a toy-car out of his pocket and he started rolling it back and forth. He didn't know who he was; he didn't know what state he was in or why he was there at that moment in time. This was the cognitive and sensorial level of a patient for whom apitherapy was the last hope. The last KPS assessment made in Germany, in the first decade of September 2010, indicated a score of 50%. In our opinion, given the deterioration of the patient's clinical state – disability, permanent need of care and specialised assistance – the score could not amount to more than **KPS – 40%**. In order to discuss the patient's evolution during apitherapy we shall mainly use, just like in the case of standard therapy, the monthly assessment reports issued by the university clinic in Germany: Starting from December 2010, the patient had to return to the clinic every month. Each assessment was accompanied by a double MRI scan: native and using contrast agents. **We shall use chronology to follow the patient's evolution during apitherapy as well.**

October 2nd 2010: the family brought the patient to our clinic, in the state described above. The only medical document they could produce was the last assessment report issued during the second half of September 2010.

² „...von der Durchführung weiterer antineoplastischer Therapien abgeraten hätten.“

³ Avastin is a concentrated substance used for an IV solution that should prevent the neoangiogenesis from carrying on, thus stopping the tumour's progression. The active substance contained in Avastin is bevacizumab, one of the numerous "mabs" in the monoclonal humanised antibody. Its "task" is to stop the growth of neo-blood vessels inside the tumour, being linked, from a properties point of view, to the vascular endothelium growth factor (VEGF). This is one of the angiogenic factors and it is located inside the walls of blood vessels and lymphatic vessels. Avastin - which is relatively frequently used, although the reported clinical cases do not warrant any proven efficiency on its part – might work as a placebo, if it didn't have so many side effects.

Although the para-clinical data⁴ was missing, at the parent's persistence, we put together an apitherapy protocol based on our previous clinical experience and we recommended an initial diet of only 30 days. The patient's obesity (126 kg at a height of 1.68 m) required a serious reduction of fat intake. We approximated the necessary liquid intake at minimum 2.5 litres/day (out of which teas made up about 1.5 litres/day).

We recommended the interruption of Avastin medication, the reduction of Methylprednisolone dose by ¼ per week while we cut the administration of carbamazepine by half in the first 10 days, and we later interrupted it altogether (the patient's mother confirmed the absence of any convulsive seizures). This is neither the time nor the place to exhaustively describe our therapeutic approach of intra-skull tumours, nor is it the time or place to exhaustively describe the bio-structure of the apitherapy substances we use or the pharmacodynamics properties of the substances we deem to have a huge antineoplastic potential. However, there is something we must specify: we are not talking about two parallel medical sciences, one for standard tumour therapy and the other one for apitherapy. The scholastically "unorthodox" apitherapy, which is still regarded rather as a heresy⁵, has tumour-fighting properties that are practically unknown to clinical experts. Undoubtedly, there are many differences between standard therapy and apitherapy, the most important ones, which can be used in favour of apitherapy being: biocompatibility and action synergy, obtained through the synergetic presence of both therapeutic agents and substances supporting their actions, both systemically and at the level of the targeted tissue or limiting their aggressiveness when necessary.

There is also a fundamental difference between standard therapy and apitherapy. Due to their aggressiveness, ***standard therapy agents*** systemically disable the body's physiological functions, along with their intended cytostatic effects, thus requiring a complex adjuvant medication.

However, in synergy with the cytostatic actions, ***apitherapy substances*** restore the functions of the immune system which thus mobilises itself and contributes to the anti-tumour fight, something that's completely missing from standard therapies.

The apitherapy substances recommended in this case were: Apicitosan II, Api Immunostim IV, Ares II and Apidigest. For sweetening the teas we recommended a mix of polyfloral types of honey, from the mountainous and sub-Carpathian area of Gorj County, Romania. The other apitherapy substances have the same origin. The bee glue used to produce the ARES II substance, collected from bees living in the bushes of Amaradia river, around the town of Bălănești, Gorj clearly has better effects than the highly appreciated Brazilian bee glue. Acting synergistically, the substances comprised in this apitherapy treatment have cytostatic, anti-inflammatory, immunostimulatory, anti-fibrosis, anti-angiogenic, anticonvulsant, anticoagulant, antiemetic, lipid-lowering and hypoglycaemic effects. Besides, these apitherapy medicines comprise all necessary substances for cell construction, functioning and protection. An exceptional advantage is the fact that apitherapy treatments offer not only the precursor substances needed for the "lucrative" functions of human metabolism, but they also comprise an impressive range of fully elaborated substances – the priceless apiarian biomolecules – which have a molecular bio-structure identical to

⁴In Germany, medical documents have a different "path" from the one used in Romania. As I said, they could only produce the last assessment report, issued in September 2010, which also informed the family that there were no other antineoplastic therapy options left. They later managed to obtain, with great difficulties, the previous assessment reports, issued prior to their return to Romania. We recommended a minimum number of lab tests but the family insisted that the sampling should be postponed for a while: the patient, who was otherwise completely absent, was strongly rejecting the presence of white medical coats and medical instruments.

⁵„Heresy” – When the patient showed up for his first reassessment, the doctors in the German clinics named it, at first, “witchcraft” – stating that it was a long way from becoming a real science. Only when pharmacology, fundamental medical research and clinical research start working together, convinced of the great importance that the “gifts” bees give us, bear for human health, an importance that is now difficult to assess, only then apitherapy shall become a medical science equal to any other science: both in universities, where it can become better known and in clinics, where it can be applied. Only then and only in this way shall apitherapy substances become a standard among what we usually call now medicines and they shall become available for widespread and beneficial use. ***However, in order for this to become reality, the interest of researchers and clinical experts has to be mobilised: we have to admit that, this is one of the purposes we aim to fulfil with the present study.*** And, besides the interest of certain “traditional” or “innovative” drug producers may also have to be mobilised.

that of synthetic molecules, submitted to exocytosis, which is very important in cases of metabolism malfunctions.

A molecular biology and immunology treaty would be needed to present, in detail, the bio-structure and the therapeutic functions of apitherapy substances. Besides our Master's programmes, we have dedicated to this subject two PhD theses in medical sciences⁶, seven books⁷, 95 studies published in medical journals⁸. One of these studies was published in 2014, in the Swiss medical journal *Molecules*⁹, and was awarded the CNCSI Prize (CNCSI = The National Council of Scientific Research in Higher Education).

November 2nd 2010 – The family brings in the first lab tests – conducted by a lab in Romania:

SPE – laboratory reference ranges

Serum Proteins %	Normal Values %	Result %
ALB	55-65	62,7
α_1	2-4	2,5
α_2	7-11	8,6
β	8-14	12,6
γ	12-20	13,6
A/G	-	1,6

TP = 7,1 g/dL (6-8); γ = 13,6% (12-20); IgG = 910 mg/dL(700-1600)
 IgM: 78 mg/dL (40-240); IgA: 125 mg/dL (70-400); IgE: 56 mg/dL (<150)
 CaT: 9,1 mg/dL (9-11); Ca²⁺: 4,14 mg/dL (4,1-5,5); **Glyc: 128 mg/dL(60-99)**
 WBC: 6,1 (4010); **Ne = 78,2%** (50-71); **Lym = 14,1%** (25-45);
 RBC: 4,75 (4,4-5,9); HGB: 14,9 g/dL (12,1-17,2); HCT: 44,4% (36,1-52)
COL: 230 mg/dL (<200); HDL: 42 mg/dL (> 60); LDL: 138 mg/dl(<100)
NSE (neuron - specific enolase): 25 ng/mL (< 16,3)
CEA (carcinoembryonic antigen): 7,72 ng/mL (< 4,3)

Code: R20/112-B6 Apitherapy Medical Center Database

October and November 2010 - The patient was not reassessed in Germany:

- the patient undertook apitherapy in Romania;
- the lab test report presented above (02.11.2010) reflects the para-clinical reality after one month of apitherapy.
- November 2010, the patient's father went to the clinic in Germany to take care of some insurance-related formalities. Besides being ironically told that he resorted to the "wizards" in Romania, he was also asked to bring his son in for reassessment once a month, from December 2010. This attitude had, however, one advantage: due to the assessment reports issued by the clinic in Germany, the patient's evolution during his apitherapy in Romania was recorded and it can now be followed in documents whose credibility cannot be doubted (which are available in our database).

- December 2010 – The assessment report issued by the clinic in Germany states:

- centrally, the tumour shows a considerable necrosis area;

⁶Andrițoiu Călin Vasile, The effects of apitherapy substances on the pathophysiological mechanisms of hepatic cirrhosis, UMF „Gr.T.Popa” („Gr.T.Popa” University of Medicine and Pharmacy, Iasi), Iași, 2009; Andrițoiu Vasile, The apitherapeutic rebalance of plasmatic proteins by rebalancing serum proteins, UMF „Gr. T. Popa”, Iași, 2012.

⁷Andrițoiu Vasile, the ABC of apitherapy, Editura Punct, Târgu-Jiu, 1995; Andrițoiu Vasile, 209 Apitherapy Recipes, Editura Nipexim, Târgu-Jiu, 1999; Andrițoiu Călin Vasile, Vasile Andrițoiu, Theses and hypotheses in apitherapy and api-diet, Casa de Editură Venus, Iași, 2010; Andrițoiu Vasile, Călin V. Andrițoiu, Cases and Clinical Studies in Apitherapy, Casa de Editură Venus, Iași, 2010; Andrițoiu Călin Vasile, Micrographs of Apiarian Products. Apitherapy in cardiovascular diseases, Editura PIM, Iași, 2014; Andrițoiu Călin Vasile, Effects of Apitherapy Products. Apiary against toxic hepatic cirrhosis, Editura PIM, Iași, 2014; Andrițoiu Călin Vasile, New natural biocompatible materials with applications in wound-healing, **Lambert Academic Publishing, Saarbrucken, Germania, 2014.**

⁸Of which: 29 B+, 5 ISI and 61 ISBN.

⁹Călin Vasile Andrițoiu, Lăcrămioara Ochiuz, Vasile Andrițoiu, Marcel Popa, Effect of Apitherapy Formulations against Carbon Tetrachloride-Induced Toxicity in Wistar Rats after Three Weeks of Treatment, **Molecules, Basel, 2014.**

- compared to the previous assessment (made in September 2010), **the tumour shows no modification tendencies**¹⁰ (thus, the tumour's progression ceased);

Still reluctant and maybe opposed by what he saw compared to what he had expected to see, the clinician did not register the beneficial changes recorded in the patient's clinical state, although they were more than obvious; but the word "wizards" was never used again either!

Therefore, after two and a half months of apitherapy in Romania, the MRI scan showed a cease of glioblastoma progression. We associated this cease of tumour progression with the reduction of immunosuppression, as well as with the antiangiogenic and antimetabolic effects of the therapeutic agents comprised in the apitherapy products manufactured by Apitherapy Medical Center.

In January 2011, after 80 days of apitherapy, the assessment report issued in Germany states:

- the tumour stopped its progression becoming stable compared to the previous examination¹¹.
- Carbamazepine and Methylprednisolone therapy was interrupted (it was requested they were resumed).

- the significant improvement of our patient's general health state is a "cognitive achievement". The patient is well oriented, cooperative and he shows no sensorimotor deficiencies¹². There is no sign of incontinence either.

Taking into consideration the data revealed by the MRI scan and the radical improvement in the patient's state, the report assesses: **„Karnofsky – Index 60%”**.

- In the current clinical state, there is still **no therapeutic option that might be efficient**¹³

- **the patient returns to Romania**, with his family, to continue his naturopathic treatment¹⁴.

Although fairly limited, the medical test report issued in Germany on 22.01.2011, gave us the opportunity to assess the patient's para-clinical evolution compared to the tests made in Romania, in 02.11.2010.

Alongside the MRI images which certify a cessation of tumour progression, the clinical examination certifies the improvement of the patient's health state as well, from KPS 40 in October 2010 to KPS 60 in January 2011, after 80 days of apitherapy.

Test Reports – 02.11.2010 –Romania	Test Report - 22.01.2011-Germany¹⁵
after 30 de days of apitherapy (October 2nd – November 2nd 2010)	after another 50 de days of apitherapy (November 2nd 2010 - January 22nd 2011)
-WBC 6.1 thousand/ μ L (4-10)	6.3 thousand/ μ L (4-10)
-RBC 4.75 mil/ μ L (3,8-5,1)	5.1 mil/ μ L (4,40-5,40)
-Lym 14.1% (25-45)	18% (20-40)
-IgG 910 mg/dL (700-1600)	not conducted
-Ne 78.2% (50-71)	68% (40-70)
-PLT 189 thousand/ μ L (150-450)	209 thousand/ μ L (150-400)
-COL 230 mg/dL (140-220)	173 mg/dL (< 200)
-LDL 138 mg/dL (<100)	101 mg/dL (<160)
-HDL 42 mg/dL (>60)	51 mg/dL (>40)
-GGT 72 U/L (15-50)	25 U/L (< 66)

¹⁰ „Infratentoriell keine Auffälligkeiten. Keine relevante Änderungstendenz im Vergleich zur Voruntersuchung bei ausgedehntem Glioblastom-Rezidiv und erheblicher Tumorausdehnung wie beschrieben im Sinne einer Gliomatosis cerebri.”

¹¹ „Aktuell: stabiler Befund bei bekanntem Tumorrezidiv.”

¹²The report describes the patient as being „orientiert und kooperativ”, „kein sensomotorisches Defizit.”

¹³ „Von unserer Seite sehen wir weiterhin keine sinnvolle Therapieoption.”

¹⁴The patient „... wird sich zur Weiterführung der naturheilkundlichen Therapie demnächst wieder nach Rumänien begeben”.

¹⁵It was the first medical test report issued in Germany that was shown to us.

-Glycaemia	128 mg/dL (60-99)	80 mg/dL (60-110)
-EPS	(see EPS above)	not conducted
-NSE	25 ng/mL (<16,3)	not conducted
-CEA	7.72 ng/mL (< 4,3)	not conducted

To summarise the evolutions recorded during the first 80 days of apitherapy:

- the family did not produce any medical test report on 02.10.2010, when the apitherapy started.
- lab tests conducted on 02.11.2010 were completed after 30 days of apitherapy, therefore they did not accurately record the patient's state at the beginning of the therapy.
- the tests conducted in Germany, on 22.01.2011, after 80 days of apitherapy and 50 days after the previous tests done in Romania (along with the information gathered through MRI scan and the clinical examinations) **confirmed**:
- **the antiangiogenic and antimitotic effects** of apitherapy products Apicitosan II and ARES II; their antiangiogenic potential made necessary the exclusion of Avastin.
- **the anti-inflammatory and anti-immunosuppressant effects** of apitherapy product: Api Immunostim IV made necessary the exclusion of Methylprednisolone¹ because, its administration could only worsen the immunosuppression state specific to GBM, thus facilitating – or even stimulating – tumour mitosis, by its immunosuppressive action. We do not know what the patient's immunity level was at the beginning of apitherapy, but it could only amount to a severe immunosuppression. The increase in IgG to 910 mg/dL and the increase of Lym to 14.1%, can only be the result of correctly approaching GBM as an immunosuppressive dysproteinaemia (please observe the continued percentage increase of lymphocytes recorded in the medical test report issued in Germany, 50 days after the one issued in Romania); *apitherapy products contain their own anti-inflammatory and immunomodulatory substances.*
- **the fat-lowering effect of apitherapy products** can be easily noticed by comparing the still high fat values recorded in the medical test report issued in Romania and their normalisation after another 50 days of apitherapy (in the medical test report issued in Germany)².
- **the hypoglycaemic effect of apitherapy products** can be noticed by comparing the two medical test reports presented above. In the absence of lab tests, we do not know the glycaemia level before the start of apitherapy but we can see that during the 50 days passed after the analyses conducted on 02.11.2010, when glycaemia was recorded at 128 mg/dL, it dropped to 80 mg/dL, becoming normal and staying normal throughout the entire therapy period and even after the therapy ended. This effect was recorded while the patient was receiving 225 grams of honey every day; the therapy products contained honey and all his teas were taken with honey as sweetener. No doubt, these statements expose us to new heresy³ accusations.

¹We have stated that we regarded GBM as the result of a dysproteinaemia marked by immunosuppression (hypogammaglobulinaemia, with the serious drop of immunoglobulins, the most obvious being the drop of IgG), at the same time as lymphopenia occurs, especially at lymphocyte T level. In apitherapy, which also has controllable anti-inflammatory properties, the anti-inflammatory effect of Methylprednisolone is no longer necessary. Through its immunosuppressant effects, this chemical synthesis corticosteroid facilitates tumour progression and lymphopenia (it increases immunosuppression at molecular and cell level).

²Hyperlipidaemia, generally accompanied by dyslipidaemia is specific to GBM, with abnormal fat accumulation at brain level. The quantitative normalisation of these fats - that reduces the efficiency if any antineoplastic therapy – can only be achieved after the normalisation of lipidaemia. The tests conducted in Germany, along with all other investigations and clinical progresses recorded, confirmed the efficiency of our therapeutic approach for GBM.

³Apitherapy has clear hypoglycaemic properties, superior to any other therapy, including when it comes to treating insulin-dependent DZ II (type 2 diabetes). Our way of treating hyperglycaemia, which may seem as “unorthodox” to clinical experts, is based on restoring the normal functions of the cell glucose and insulin receptors, on restoring phospholipases functions and on other insulin-like factors existing in the apitherapy products manufactured by Apitherapy Medical Center. All medical studies about hyperglycaemia recommend the exclusion of honey from the daily diet of hyperglycaemic/ diabetic patients. But still, if our patient ate 225 grams of honey per day and still, his glycaemia normalised, this was due to the insulin-like factors contained in the apitherapy products. There is also another aspect that has to be kept in mind: these hypoglycaemic agents are contained in the same viols as the anti-tumour therapeutic agents. This way, the presence synergy insures the action synergy of certain bio-compatible substances,

- **The anticonvulsant effect of apitherapy products**, which occurs synergistically to all other effects and is superior to the effect of Carbamazepine, is confirmed by the absence of any convulsive seizure, something that was later also confirmed by the assessment reports written in Germany.
- **The effect of restoring the entire body's physiological functions**, - which is easily noticeable by comparing the medical tests mentioned above and is also associated with a radical improvement of the patient's clinical state, - render any adjuvant therapy useless. Once restored, these physiological functions mobilise themselves to help fight against the tumour.

On returning to Romania, together with his mother, the patient continued his apitherapy. During a visit to our practice, I was under the slight impression that his state was regressing compared to the one recorded in mid-January (when he was preparing to go to Germany for reassessment). Then, the patient told me that, upon insistence from the doctor in Germany, he had resumed the Carbamazepine and Methylprednisolone administration (the recommendation to resume the administration of these two drugs, which we had excluded, were recorded on each monthly assessment report). Through its aggressiveness, Methylprednisolone can quickly redirect the evolution towards immunosuppression. In order to verify this, I requested a set of tests.

SPE – Laboratory reference ranges (Romania) – 07.02.2011

Serum proteins%	Normal values %	Result%
ALB	52-68	65,3
α_1	2-5	2,8
α_2	6,6-13,5	10,1
β	8,5-14,5	11,9
γ	11-21	9,7
A/G	1,39-2,23	1,9

TP = 6,54 g/dL (6,6-8,7); IgG: 705 mg/dL (700-1600);
 CaT: 9,2 mg/dL (8,6 – 10,2); Ca²⁺: 4,04 mg/dL (3,82-4,82)
 WBC: 9,32 thousand/ μ L(4-10); Ne: 76% (42-75); Lym:13.4% (20-40);
 RBC:5,13 mil/ μ L(4.3-5.7);HGB:16,7g/dL (13-17.3); HCT: 49.5% (39-49)
 Out of the total Lym, which dropped to 13.4%:
 LymB: 19% (7-21); LymT: 59% (61-84);
 Lym Th-CD4+: 31% (32-60); Lym NK: 12% (10-30); 176/ μ L (210-740); Lym NK activated: 1.4% (<17); 2/ μ L (<40);

Code: R20/112 –B6, Apitherapy Medical Center database

The immunosuppressant effect of Methylprednisolone, which is a disadvantage in the antineoplastic treatment of a cancer that is already characterised by immunosuppression, was indeed confirmed. Compared to the previous lab tests:

- globulin γ , an immunosuppression indicator, dropped from 13.6% to 9.7% (11-21);
- IgG – the most important immunoglobulin, dropped from 910 mg/dL to 705 mg/dL (700-1600);
- neutrophils became again aggressive, increasing from 68% to 76% (42-75);
- the drop of lymphocytes from 18% to 13.4% (20-40) in only three weeks of methylprednisolone administration is relevant for the drug's immunosuppressant potential. The drop of a Lym Th-CD4+ under its minimum threshold: 31% (32-60), was accompanied by a dramatic decrease of NK activated lymphocytes to 1.4% (< 17), their number amounting to only 2/ μ L (<40).

Faced with this new decline in the patient's immunity, I requested once again the cease of Carbamazepine and Methylprednisolone treatment. I also asked the patient to show the doctor in Germany this last medical test report, at his next reassessment.

February 2011, the assessment report in Germany states:

- The stability of tumour relapse⁴ (the absence of tumour progression)
- The therapy conducted in Romanian led to a significant improvement of the patient's general clinical state
- He no longer suffers from incontinence, he is normal from a cognitive point of view, he is alert, well oriented, cooperative and with no signs of sensorimotor deficiencies.

bearing mutually complementary actions. The hypoglycaemic agents are synergistically associated with the fat-lowering effect of the apitherapy agents.

⁴ „Aktuell: stabiler Befund bei bekkantem Tumorrezidiv”.

- The report recommends, again, the resumption of Carbamazepine and Methylprednisolone administration;
- Assessment: „**Karnofsky-index 70%**”
- The report states that: “***we continue to see no reasonable therapy option***⁵”
- The patient continues his naturopathic therapy in Romania⁶; he returns for a re-assessment after three months. This assessment report was communicated to the other German clinic as well. But this time, the doctors’ trust in the „*naturheilkundlich*” conducted in Romania, was obvious. Once he got over the surprise of seeing such a positive patient evolution obtained through therapeutic means other than the standard methods and seeing that these results remain so stable, the clinical expert decided not to recall the patient for assessment every month anymore, but once every three months. The increase of KPS from 50% in September 2010 (at which time, the clinics in Germany had informed the patient’s family that there were no efficient therapy options left) to 70% - a figure that was assessed by prestigious clinics in Germany, after four and a half months of apitherapy (in February 2011) - validates:
- our theory regarding the approach of glioblastoma as an immunosuppressant type of dysproteinaemia succeeding autoimmune dysproteinaemia.
- the tumour fighting potential of apitherapy products.

The patient returned to Romania where he carried on his apitherapy until May 2011, when he went to Germany for re-assessment.

Due, probably, to the clinical expert’s curiosity towards the means and effects of our method, the patient was recommended a set of tests comprising, among other things, both SPE and glycosylated haemoglobin (following the surprise of seeing a hyperglycaemia remission through apitherapy).

Medical Test Report - May 2011 (Germany)

SPE – laboratory reference ranges

Serum Proteins%	Normal Values %	Result %
ALB	59-70,6	65,3
α_1	2,1-4,4	4
α_2	5,2-9,7	8,6
β	7,3-12,2	10,3
γ	11,2-19,9	11,8
A/G	-	1,88

TP = 6,96 g/dL (6,50-8); ALB = 4,54 g/dL (3,80 – 5,90)

γ = 11,8% (11,2-19,9)

Ca = 4,87 mval/L (4,20-5,20)

WBC: 7000/mm (4000-10000); Ne: 68% (40-70); **Lym: 18%** (20-40)

RBC: 5,2 (4,40-5,90); HGB: 17,5 g/dL (13,3-17,7)

HCT: 50,2% (40-52); PLT: 202 000 (150-400)

Blutzucker: 85 mg/dL (60-110); HbA1c: 5,2% (< 6,1)

COL: 180 mg/dL (<200); HDL: 54 mg/dL (>40);

LDL: 109 mg/dL (< 160); TRG: 105 mg/dL (< 160)

Code: R20/112-B6, Apitherapy Medical Center database

This medical test report preceding the MRI scan shows:

- the normalisation of TP and SP (proven by SPE), with the return of globulin γ ⁷ within normal values.

⁵ „***Von unserer Seite sehen wir weiterhin keine sinnvolle Therapieoption***”.

⁶ „***Herr... wird sich zur Weiterführung der naturheilkundlichen Therapie demnächst wieder nach Rumänien begeben***”.

⁷Globulin γ is a good immunity indicator: ***in physiological immunity***, under homeostasis conditions, when the γ value is recorded at or around halfway between the minimum and the maximum threshold (for instance, the determined value of globulin γ , compared to the n.v. limits of the Germany lab -11,2-19,9 mg/dL- should be around 15,55 mg/dL); ***in autoimmunity***, the value of globulin γ grows close to, especially going over the maximum n.v. threshold; ***in immunosuppression***, the value of globulin γ drops to or under the minimum threshold of n.v.. In this case, after one month of apitherapy and by excluding Methylprednisolone, we brought γ to 13,6 mg/dL, and lymphocytes to 14,1%: after another 50 days, the tests conducted in Germany recorded the increase of lymphocytes to 18% (20-40).The resumption of Methylprednisolone administration led, in a very short period of time, to the resumption of the

- the stabilisation of lipidaemia within normal values.
- glycaemia steadiness: this time, the patient is recommended a glycosylated haemoglobin test as well, which comes back within normal values - HbA1c = 5,2% (< 6,1) - just like the glycaemia test, despite the 225 grams of honey the patients eats every day.
- the blood count values are also recorded within normal limits, except for lymphocytes, but they too are approaching the normal value, as the γ comes back to normal (although they are near the lower limit).

June 2011, the assessment report in Germany states:

- „Aktuell: stabiler Befund bei bekanntem Tumorzidiv“;
- the MRI scan shows a “relatively similar” state to the one recorded in February 2011
- the patient is alert, well oriented and he shows no sign of sensorimotor deficiency;
- he suffers no epilepsy seizures, although he takes no anticonvulsant⁸ treatment.
- the unexpected progress made by the patient is due to the diet⁹ kept in Romania
- the need to resume the Carbamazepine treatment is discussed with the patient and his father.
- the **appropriateness of a new surgery** is also discussed, but the idea is not accepted by the patient or by his father.
- assessment: „**Karnofsky – Index 70%**“
- he returns to the clinic for **a new re-assessment after 3 months.**

The fact that the tumour relapse is “stable” and “relatively similar” to its state recorded in February 2011, which was stated in the assessment report based on the MRI scan, is extremely relevant here: **the proliferative mitosis had been prohibited through apitherapy.** The oedema is not even mentioned anymore. The clinical examination, along with the description comprised in the assessment report issued in June 2011, stating a “Karnofsky Index 70%”, show that the tumour’s compression on the brain had become so limited that nothing in the patient’s state and behaviour indicated any compressive or infiltrative affection. ***The only thing that could explain the fact that a new surgical operation was again brought into question, was the retreat of the multiple tumour infiltrations, with evolution towards tumour encapsulation.***

The man that showed up for reassessment at the German clinic in June 2011, was no longer the suffering patient, completely detached from reality, that had showed up to our clinic, for apitherapy, in October 2010. His body weight had dropped from 126 to 75 kg. He was able to walk, to move, to comment on any topic brought into question. He was laughing when jokes were told. He was even telling jokes himself. He was missing his country, his relatives, and his friends. He had plans for the future and he was talking about returning aboard a ship. After the assessment, the

immunosuppression process, which was confirmed by the tests conducted on 07.02.2011, in Romania: γ dropped to 9,7 mg/dL (11-21), while lymphocytes dropped to 13,4% (20-40). Once Methylprednisolone was excluded again, the course towards immunity restoration was confirmed: γ = 11,8 mg/dL; Lym: 18%.

⁸ „Ihm gehe es insgesamt gut. Epileptische Anfälle seien nicht aufgetreten. Eine antiepileptische Therapie nehme er nicht mehr eine.“

⁹ „Durch eine Ernährungsumstellung habe sich nach Angaben des Vaters der Zustand des Patienten deutlich gebessert.“ The attitude of the German clinical expert towards the superior results obtained through apitherapy is no different from that of other doctors, from other countries. Our therapy protocols – constructed depending on the patient’s clinical and para-clinical evolution – were presented to him every time the patient went to his clinic for re-assessment. Obviously, diet plays a very important part in the treatment. But the successes obtained – with a KPS increase from 40% to 70% - cannot be explained by diet alone. This total lack of interest towards the therapeutic agents comprised in apitherapy products, which have clearly proven to be superior to Temodal, to radiotherapy and to numerous adjuvant medicines, does not serve the best interest of the patients at all. ***Anyway, I have not seen reported anywhere in the entire medical literature, any case of relapsed glioblastoma, to regress from KPS 40 to KPS 70, regardless of the therapy used.***

patient came back to Romania, but only for a month. Neither our arguments nor his family's pleas could temper his eagerness to return home. He felt full of life. He was eager to return to everything meaningful in his life, to his familiar environment. In July 2011, he left taking with him two months worth of apitherapy products and he promised to return to our clinic after the assessment scheduled in Germany, for September. He did not return.

The steadiness of cytostatic effects produced by apitherapy: July 2011 – April 2012

Once he returned home to Germany, in July 2011, the predictable happened. The patient started neglecting the rhythmicity of apitherapy treatment, only following it with huge gaps and upon insistence from his family. He often went out with his friends, and, during these outings, he drank beer and he ate, mostly sausages. He also started smoking again. As his mother informed us, he sometimes returned home, only towards the morning.

He didn't even want to hear about returning to Romania, where his chances of "escaping" a well-ordered lifestyle were limited. The general state of well-being that he experienced did not worry him enough to follow the apitherapy protocol strictly or to adopt a lifestyle that would prevent a new tumour relapse.

Unfortunately, after he left Romania, we received no more assessment reports from the German clinic. Then, from mid-August 2011, the patient ceased his apitherapy treatment anyway.

September 2011 - An MRI scan report from Germany states:

- The tumour is stable compared to the MRI scan conducted in June 2011
- ***Medical test report, Germany:*** the relevant biological parameters (which we won't mention again) are stable, similar to the ones recorded in the medical test report issued in Germany in May 2011, *but there are two evolutions that draw our attention:*
- *The lymphocytes increased, reaching a normal value for the first time: 25% (20-40);*
- *In the absence of apiarian sugars, glycaemia dropped: 71 mg/dL¹ (60-100);*
- ***we did not receive the assessment report from Germany*** so we don't know the KPS score.

Thus, in September 2011, the tumour had not yet resumed its progression, which means that mitosis was still prohibited by the complex cytostatic, antiangiogenic and imunomodulating effect of apitherapy products.

In February 2012, we received another lab test report: the vast majority of parameters remained stable, which proved the persistence of apitherapy effects, even after the treatment was interrupted.

February 2012, Germany – Lab Test report:

SPE – laboratory reference ranges

¹We remind you that, after a month of apitherapy, the patient's glycaemia was 128 mg/dL (we do not know its value before the start of the therapy). After another 50 days of apitherapy, it was kept within the range of 80-85 mg/dL, until September 2011, although the patient was eating about 225 grams of honey per day. There is no doubt about the normalisation of glucidic metabolism during apitherapy – under the influence of the insulin-like factors comprised in the apitherapy agents used: This is also proven by the drop of glycaemia, to 71 mg/dL once the apitherapy products ceased to be administered: the glucid metabolisms continued to remain normal, glycaemia being dependent only on the food carbohydrates intake. This drop, compared to the importance of glucose for the brain's appropriate function, leads to a drop in the brain's potential to handle the illness. From our clinical experience, we know that the brain's normal feeding and energising function corresponds to a glycaemia of or around 80 mg/dL.

Serum Proteins %	Normal Values %	Result %
ALB	59-70,6 ²	67,6
α_1	2,1-4,4	3,8
α_2	5,2-9,7	8,3
β	7,3-12,2	9,6
γ	11,2-19,9	10,7
A/G	-	2,02

TP = 6,57 g/dL (6,5-8); ALB = 4.44 g/dL (3,80-5,90)
WBC = 7000 (4000-10.000); Ne = 69% (40-70); **Lym= 20%** (20-40)
RBC: 5,2 (4,40-5,90); HGB: 16,7 g/dL (13,3-17,7); HCT: 49.9% (40-52)
PLT = 166 (150-400); **FBG = 442 mg/dL** (200-400)
Ca²⁺ = 4,55 mval/L (4.20-5.20); Glyc: 77 mg/dl (60-110)
Na = 144 mmol/L (135-148)
COL = 163 mg/dL (<200); TRG: 122 mg/dl (<170)

Code: R20/112-B6, Apitherapy Medical Center database.

Compared to the medical test report issued in February 2011, most relevant values indicate a tendency towards the restoration of immunosuppression, although they are mostly lower: **globulin γ drops** below the minimum n.v. limit: 10,7 mg/dL (11,2-19,9); **lymphocytes drop** to the minimum n.v. threshold: 20% (20-40). But, at the same time, ALB and Ca start increasing again, which can be worrying.

We spoke to the patient and to his family over the phone about the risks of “slipping” into immunosuppression, which could lead to the resumption of mitosis and thus, to the resumption of tumour progression.

The general state of well-being that he was experiencing did not prompt the patient to resume apitherapy and the diet, nor did it prompt him to talk to the clinician about a possible new surgery. In case of GBM, there is no better opportunity for such surgery, than the one offered by the lack of proliferative mitosis. **And in this patient’s case, which was unique in the history of surgeries, apitherapy provided this opportunity.**

We have no other information related to the patient’s clinical and para-clinical evolution, except for an MRI Scan Report issued in April 2012.

April 2012, an MRI Scan Report in Germany, states:

- The tumour resumed its progression (compared to the previous scan)
- Compared to the scan conducted in June 2011, the oedema re-occurred
- Multiple marginal tumour necrosis occurred as well.
- There was also a slight increase of compression over the ventricles.

After this MRI scan report, we received no other medical document, neither from the radiology office nor from the clinic – and we are referring to assessment reports – neither have we received any lab test reports. In the absence of any medical documentation, we end our presentation here. All our subsequent information was limited to telephone communications with the family. In May 2012, the standard therapy was resumed. A few months later, in September 2012, the patient’s clinical state went back to the one recorded in September 2010 when he came to Romania for apitherapy. Shortly afterwards, the glioblastoma defeated the patient for good.

²With regards to the percentage values of ALB within SPE, we concluded from our clinical experience that this valuable protein should neither drop below 60% nor increase over 66% (except for certain minimal deviations and only when each of the globulins α_1 , α_2 , β and γ have normal values). In Romania and in Germany, as well as in other countries, SPE is rarely used for diagnosis purposes or for monitoring therapy efficiency, regardless of the therapy used. Besides, the reference values of normal limits are very different from one lab to another. Anyway, regarding SPE, it would be very difficult if not impossible for a clinical expert to report the case of a healthy patient, with an ALB amounting to over 70% of the total SP. Besides, the fact that hypoalbuminemia plays no role in the diagnosis process, is also true. In reality, percentage hypoalbuminemia (determined through SPE) is involved in many diseases, some of which amounting to invalidity state (brittle bone disease, ichthyosis, etc) but it can also be an evolution marker towards intra-skull cancers.

Discussions

The patient's evolution during the standard therapy (January 2006 – September 2010), can only be followed through the assessment reports issued in Germany, that we had quite a lot of trouble obtaining.

At the age of 34.5, in the winter of 2005, the patient started experiencing forehead pains that became more and more intense and frequent over time. We do not know in what stage the glioma was at that time (whether it was benign or at the beginning of its cancerisation process). One year later, at the age of 35.5, in January 2006, the patient underwent surgery, for the resection of the primary tumour, which had been directly diagnosed as level 4 GBM. The patient then went through the standard therapy, with Temodal, radiotherapy and adjuvant therapy. In May 2009, three and a half years after the first surgery, an MRI scan showed the occurrence of tumour relapse, for which, the patient was operated on again, in June 2009. In July 2010, his state was assessed as being the equivalent of KPS – 100. However, soon afterwards, a second relapse, which was more aggressive and more invasive than the first, seriously worsened the patient's state: in September 2009, when the patient became absent from a cognitive point of view, he was assessed at KPS – 50, and his family was informed that there were no more antineoplastic treatments left to use that would be efficient against such level of GBM evolution.

Therefore, four and a half years had passed from the beginning of therapy until it was concluded that the patient could no longer be treated (January 2006 – September 2010).

We think that this survival period, which is quite long compared to most GBM cases, was due to the doctors' professionalism and to the patient's young age. However, any therapy has its limits, and the GBM therapy is famous for its purpose, ie. extending the patient's life.

The patient's evolution during apitherapy (October 2010 – July 2011) as well as the persistence of this therapy's effects after the treatment was interrupted (August 2011-April 2012) is what we call a novelty compared to all other GBM cases: ***the mitosis prohibition and the tumour remission.***

Due to his "encounter" with apitherapy, the patient was given the chance to an unusual evolution, totally different from the normal evolution recorded in similar tumour cases.

Brought to Romania by his family, the patient went through an apitherapy treatment for his tumour, from October 2nd 2010, until July 2011, which he continued in Germany until August 2011, although not in a very strict manner. Overall, he underwent ten months of apitherapy, if we subtract the time spent on his trips to the clinic in Germany where he had been called for reassessments.

The interruptions of apitherapy treatment, during these trips to Germany or the fatigue that came with them, could not facilitate the tumour remission. But they did come with a very important advantage: the apitherapy effects were assessed in medical documents that could not be doubted: lab test reports, MRI scan results and assessment reports issued by German medical institutions (that had been treating the patient since 2006). All these documents are available in the Apitherapy Medical Center database, under the reference previously mentioned¹.

In October 2010, when the patient started his apitherapy, we assessed him at KPS-40: he was suffering from incontinence, from a disabling sensorimotor deficiency, he was absent from a cognitive point of view, he was suffering from severe headaches and from epileptic seizures; he was weighing 126 kg, at a height of 1.68m; he was under anticonvulsant, anticoagulant, anti-inflammatory and immunosuppressant treatment, while his anti-tumour treatment was reduced to the antiangiogenic medicine Avastin (whose side effects are better known than the effects it should have as an antiangiogenic drug), since other therapies were no longer applicable in his state.

¹Code: R20/112-B6

In the absence of any para-clinical data, when we set the apitherapy treatment, we had to rely on the similarities of this case, with other GBM patients who had resorted to apitherapy when they were given no other chance.

The standard therapy had been focused on one single target: the tumour. But, through its effects, it had increased the existing metabolic unbalances, as well as triggering new ones. These unbalances impeded on the tumour-fighting potential of the standard therapeutic agents, whose aggressive side effects were very severe anyway.

In this situation, an old Thracian medical principle was applicable: you cannot heal a part without healing the whole and you cannot heal the body without healing the soul². According to our method, the neoplastic action of the agents comprised in the apitherapy products that we manufacture ourselves has to be supported by the systemic restoration of physiological functions in the entire body. The complexity of substances contained in apitherapy products, which is different from any other therapeutic method or mean due to its presence and synergy action, provides not only a huge tumour-fighting potential but also the opportunity to restore metabolic functions that once normalised, can help fight the tumour themselves.

We remind you that we see GBM as an atypical immunosuppressant dysproteinaemia: it is characterised by an increase of ALB and Ca²⁺, with an aggressive mitosis, generally accompanied by immunosuppression: B and T lymphopenia, a dramatic drop of NK cells, hypoglobulinemia γ and hypoimmunoglobulinemia, especially at IgG level.

In order to follow with more ease, the patient's para-clinical evolution during apitherapy and the stability of the apitherapy results, after the treatment was interrupted, we drafted a "summarising table of the patient's para-clinical, imaging and clinical evolution during apitherapy (October 2010 – April 2012)"

From a para-clinical point of view, the case can only be followed between November 2010 (the first medical test report issued in Romania) and February 2012 (the last medical test report received from Germany). After a month of apitherapy (October 2010), when the patient's clinical state had visibly improved, on November 2nd 2010, the patient was submitted to his first lab tests in Romania. Thus, the biological parameters determined now, were not the exact ones he had when he had been brought in from Germany. In the process of rediscovering his balance, the patient still showed: dyslipidaemia (COL - 230 mg/dL; LDL -138 mg/dL); HDL - 42 mg/dL), hyperglycaemia (128 mg/dL), liver dysfunctions (GGT- 72 U/L), neutrophilia (78.2%), lymphopenia (14.1%), immunosuppression (γ - 13,6%; IgG - 910 mg/dL), and the positivity of tumour markers NSE (25 ng/mL) and CEA (7.72 ng/mL).

The apitherapy efficiency, judged from the lab-test perspective, is beyond any doubt: the first set of lab tests conducted in Germany showed *a normalisation of the biological parameters. These parameters remained stable, within normal range, even in February 2012*, when we received our last medical test report from Germany (see the Summary Table). The normalisation of patient's glycaemia, which was surprising³ under the apitherapy conditions, was checked in

²Healing the patient's "soul" was out of the question, given the state of cognitive absence he was in. In the first stage, we had to "win over" the family members and convince them to trust the anti-tumour potential of apitherapy products. They confessed to having resorted to apitherapy, following a suggestion from a lady in Germany, who was a university professor and who had a systemic erythematosus lupus forced into remission through apitherapy. As they later told us, when they first came to us the trust they had in our method was limited to making sure they had tried everything they could to save their son, so they could have a clear conscience, as parents. Since they had no medical training at all, they had to observe the positive evolution occurred in their son's cognitive state and in his behaviour, in order to really trust the process.

³The clinician in Germany was surprised to see the patient glycaemia normalise, given the fact that the patient was taking 225 grams of honey per day. To us, this was something normal – it is a normal evolution even in cases of insulin-dependent patients. The functional normalisation of insulin and glucose cell receptors, the presence of insulin-like factors in apitherapy products and the synergy of restoring physiological lipidemia, give us the opportunity to remind you the old principle employed by antique Dacian healers: you can only heal a part if you heal the whole. In our therapy strategy, which was based on a different means and logic than the standardised one, the normalisation of glycaemia and lipidemia was explained by the neoplastic efforts made by the anti-tumour agents comprised in our apitherapy products. Clinical experts know: the brain's fatty structure is normal in GBM. Mobilising and gradually reducing fats at brain

Germany as well: the lab test reports issued in January and May 2011, also determine the glycosylated haemoglobin: its values have always been normal (5.2%, n.v. being < 6.1%).

The tumour markers which were positive in November 2010 were recorded negative in February 2011.

When it comes to the patient's para-clinical evolution, we must take a closer look at the evolution of neutrophils, lymphocytes, globulin γ and immunoglobulin IgG. For this, however, we must keep in mind that immunosuppression is a feature of GBM, which facilitates inflammations and erodes the immune resistance of the body not only in the face of the tumour but also in the face of the adverse effects brought about by standard antineoplastic therapy.

The Methylprednisolone anti-inflammatory therapy is, at the same time, an immunosuppressive therapy as well, applied to a disease that is itself accompanied by immunosuppression. We do not intend to open a debate on the anti-inflammatory effects of apitherapy *versus* Methylprednisolone, but we cannot ignore such a discussion either.

Through its anti-inflammatory and immunosuppressant effects, Methylprednisolone stimulates PMN neutrophils acting on the inflammation site, but it cannot control or limit their aggressiveness and it does not have the potential to eliminate the effects of oxidative stress. Besides, through its immunosuppressant effect, the drug actually facilitates inflammation: the rise of PMN neutrophils during the administration of Methylprednisolone is accompanied by a drop of B lymphocytes (thus affecting the humoral mediated immunity), of T lymphocytes (thus affecting the cell mediated immunity), of NK cells, as well as by a drop of antibody synthesis (the level of globulin γ drops), the level of the most valuable type of globulin – IgG - being particularly low (for their evolution, see the Summarising Table).

Therefore, in this case, the administration of Methylprednisolone not only reduced immunity which was already compromised, but it also increased inflammation (which was confirmed by the increase of neutrophils over the n.v. limit, at the same time as the immunosuppression worsened – immunosuppression that was easily detectable due to a drop of lymphocytes, globulin γ and IgG).

Through their anti-inflammatory and immunomodulatory effects, apitherapy products proved to be clearly superior to Methylprednisolone. Every time we excluded Methylprednisolone from the medication, neutrophils went back to normal, lymphocytes gradually grew while globulin γ and IgG reached normal ranges.

In the absence of any lab test results from Germany, we do not know the levels of these parameters before apitherapy started. However, the lab test reports issued later are relevant for their subsequent evolution:

In October 2010, the patient underwent apitherapy. During this month, we first excluded Avastin, then, two weeks later, we excluded Carbamazepine and we reduced the Methylprednisolone dose by $\frac{1}{4}$ per week (the last $\frac{1}{4}$ was administered on November 1st 2010);

November 2nd 2010, precisely 1 month into apitherapy, the first lab test report issued during apitherapy showed the neutrophils values still high (78.2%, while n.v. was 50-71) but, after analysing their subsequent evolution, we assume that, before apitherapy started, this value must have been even higher; lymphocytes, which were recorded at normal values only in the last lab test report issued in Germany (February 2012) increased to 14.1% (25-45); the level of globulin γ grew to 13.6% (12-20), while IgG grew to 910 mg/dL (700-1600);

level, supports the tumour-fighting action. The normalisation of glucid metabolism, along with the normalisation of lipid metabolism, allow the brain to access a normal glucose quantity deeply needed for its energy-functional functions.

In January 2011 (during the months of December 2010 and January 2011, the patient stopped taking Methylprednisolone) the lab test report (from Germany) showed the ***normalisation of neutrophils*** to 68% (40-70), ***while lymphocytes grew to 18%*** (20-40). The German lab did not conduct SPE or immunoglobulin tests (therefore, we do not know the values of γ and IgG). Upon request from the clinic in Germany, which was also recorded in the assessment report, the patient resumed the administration of Carbamazepine¹ and Methylprednisolone for three weeks, from January to February 2011.

Aware of the effects that these drugs could have, I immediately requested a set of lab tests.

As you can see from the lab test results in February 2012, in only three weeks of administration, Methylprednisolone led to an increase of neutrophils over the upper limit of normal values to 75,9 (42-75). At the same time, lymphocytes dropped to 13.4%² (20-55) and globulin γ also dropped to 9.7% (11-21) as well as IgG to 705 (700-1600). Again, we stopped the administration of Carbamazepine and Methylprednisolone and the ***lab tests conducted in Germany in May 2011*** proved this measure to be correct: neutrophils dropped to normal values again - 68% (40-70), lymphocytes grew to 18% (20-40), globulin γ grew to 11.8% (11.2-19.9). Although the first SPE was then conducted in Germany, in response to the lab test reports received from Romania, immunoglobulin levels were not determined.

As we said before, we do not intend to start a debate on apitherapy *versus* Methylprednisolone. However, the lab test results and the positive evolution of the patient's clinical state when Methylprednisolone was excluded raise questions regarding the efficiency of this drug in treating GBM: it had actually stimulated the inflammation and had reduced the tumour fighting potential of lymphocytes so, given these effects, it could even be accused of facilitating tumour progression.

On the other hand, apitherapy products have clearly proven their anti-inflammatory, immunomodulatory and tumour-fighting potential. It is not another heresy towards the scholastic religion of standard therapies, using chemical drug substances – to normalise carbohydrate metabolism through apitherapy. Unlike synthetic cortical-therapy drugs, of pharmacy-chemical production, apitherapy products contain not only glucocorticoid anti-inflammatory substances but also other types of anti-inflammatory agents, such as MCDP³ (Mast Cell Degranulating Peptide) as well as substances capable of controlling and limiting the action of PMN⁴ neutrophils at the

¹Useless, because the patient suffered no epileptic seizure since he started apitherapy in October 2010.

If it is administered without being needed, Carbamazepine itself can cause convulsive seizures. Besides, its list of side effects is not exactly short. Nor is its list of negative interactions with other drugs.

²If Methylprednisolone can have autoimmune effects (hypergammaglobulinemia – with antibodies turning positive), its effects in terms of immunosuppressive diseases (hypogammaglobulinaemia – with antibodies deficit) seem to be less known. The effects of this corticosteroid on immunosuppression do not recommend it to be used in treating GBM, which is a disease already characterised by immunosuppression. If the drug is administered, lymphocytes drop to 13.4%, thus gravely reducing the level of humoral and cell mediated immunity. The corticosteroid seems to seriously affect the functions of the natural immune system, dramatically reducing the number of Natural Killer (NK) cells. These cells, just as cytotoxic lymphocytes, act against the tumour cells, before B and T lymphocytes, without the activation of the major histocompatibility complex (MHC) being necessary. Some recent research have shown the NK lymphocytes' potential to develop immunological memory. With help from certain substances (perforins), NK cells attack and eliminate tumour cells by creating pores in their membranes while, with the intervention of other substances (granzymes), they deteriorate the DNA in the tumour cells' nucleus, triggering apoptosis (programmed cell death). In case of a normal immunity, NK lymphocytes make up 15% of the total number of lymphocytes. The severe lymphopenia caused by Methylprednisolone is obvious in the lab test results issued in February 2011, when the total number of lymphocytes dropped to 13.4%, and, within this percentage, NK lymphocytes represented only 1.4% (in case of normal immunity, activated NK lymphocytes represent around 17% of the total number of lymphocytes; Numerically, they amounted to only 2/ μ L, while the normal value stood at about 40/ μ L).

³This substance has anti-inflammatory effects 100 times stronger than any synthetic corticosteroid.

⁴PMN hold a high oxidative potential. Once the antigen is destroyed, in the eventual absence of anti-oxidants that could limit or stop their actions, PMN keep releasing oxygen free radicals (RLO) and proteolytic enzymes which can aggravate injuries at the action site. Through their own anti-inflammatory effects, the glucocorticoids comprised in apitherapy products limit the number and access of PMN at the inflammation site. The anti-oxidants contained within the apitherapy products, especially the superoxide dismutase (SOD) and the catalase, neutralise RLO at the inflammation site, thus stopping the aggression of PMN. Through their efforts to restore physiologic immunity,

inflammation site (all anti-oxidants known by the medical sciences, especially the priceless superoxide dismutase (SOD) and catalase⁵)

However, they act complementary to other substances holding clear tumour-fighting properties, such as 10-hydroxy-2-decenoic acid to activators of tumour necrosis factors TNF- α etc.

**Table Summarising the patient's para-clinical, imaging and clinical evolution:
October 2010 – April 2012**

Test	Romania November 2010 (after 30 days)	Germany January 2011 (after 80days)	Romania February 2011 (after 96 days)	Germany May 2011 (after 186 days)	Germany February 2012 (after 466 days)	APITHERAPY 02.10.2010- August 2011
WBC thou/ μ L	6,1 (4-10)	6,3 (4-10)	9,32 (4-10)	7 (4-10)	7,3 (4-10)	KPS Evolution September 2010-June 2011
RBC mil/ μ L	4,75 (3,8-5,1)	5,1 (4,4-5,9)	5,13 (4,3-5,7)	5,2 (4,4-5,9)	5,3 (4,4-5,9)	September 2010 KPS-50%
HGB g/dL	14,9 (12,1-17,2)	16,8 (13,3- 17,7)	16,7 (13,2- 17,3)	17,5 (13,3-17,7)	16,6 (13,3-16,7)	October 2011 KPS-40%
HCT %	44,4 (31,6-52)	49,3 (40-52)	49,5 (39-49)	50,2 (40-52)	51 (40-52)	January 2011 KPS – 60%
PLT Thou/ μ L	189 (150-450)	209 (150- 400)	155 (150-450)	202 (150-400)	185 (150-400)	February 2011 KPS-70%
LYM %	14,1 (25-45)	18 (20-40)	13,4 (20-55)	18 (20-40)	20 (20-40)	June 2011 KPS-70%
NE %	78,2 (50-71)	68 (40-70)	75,9 (42-75)	68 (40-70)	65 (40-70)	Tumour evolution October 2010- April 2012
LT mg/dL	-	-	622 (400-700)	-	-	October 2010 Maximum spread
COL mg/dL	230 (140-220)	173 (< 200)	180 (< 200)	180 (< 200)	169 (< 200)	December 2011 In remission
HDL mg/dL	42 (>60)	51 (> 40)	46,8 (>60)	54 (> 40)	-	January 2011 In remission
LDL mg/dL	138 (<100)	101 (< 160)	108 (< 100)	109 (< 160)	108 (< 160)	February 2011 Maximum remission

apitherapy products activated not only B, T and NK lymphocytes but also physiologic immunity antibodies (globulin γ starts going up).

Besides, at microglia level, the production and tumour-fighting actions of the tumour-necrosis factor (TNF α -) is stimulated while also controlling its inflammatory-facilitating effects, at the same time. Additionally, apitherapy products comprise all substances needed for the construction, functionality and protection of cells, both of the glycocalyx and the extra-cell environment (MEC).

⁵SOD and catalase have a synergistically - complementary action. Apitherapy products provide all amino-acids and all minerals (Cu, Zn, Mn) needed for the biosynthesis of SOD and catalase, by use of functions specific to human metabolism. However, what is very important is the fact that apitherapy products provide SOD and catalase biomolecules identical to those obtained through organic metabolic biosynthesis.

VLDL mg/dL	-	-	25 (< 30)	-	-	02.2011- 04.2012 The tumour is stable
TRG mg/dL	-	-	127 (< 150)	105 (< 170)	84 (< 170)	April 2012 The tumour re- becomes invasive
GLYC mg/dL	128 (60-99)	80 (60-110)	82 (60-99)	85 (60-110)	77 (60-110)	Body weight evolution
HBA1c %	-	5,2 ($< 6,1$)	-	5,2 ($< 6,1$)	-	October 2010 126 kg
GGT U/L	72 (15-50)	25 (< 66)	33 (< 60)	42 (< 66)	26	December 2010 110 kg
TP g/dL	7,1 (6-8)	-	6,54 (6,6-8,7)	6,96 (6,50-8)	6,57 (6,50-8)	January 2011 107 kg
ALB g/dL	-	-	-	4,54 (3,80-5,90)	4,44 (3,80-5,90)	February 2011 101 kg
ALB %	62,7 (55-65)	-	65,3 (52-68)	65,3 (59-70,6)	67,6 (59-70,6)	June 2011 75 kg
α_1 %	2,5 (2-4)	-	2,8 (2-5)	4 (2,1-4,4)	3,8 (2,1-4,4)	September 2011 81 kg
α_2 %	8,6 (7-11)	-	10,1 (6,6-13,5)	8,6 (5,2-9,7)	8,3 (5,2-9,7)	February 2012 97 kg
β %	12,6 (8-14)	-	11,9 (8,5-14,5)	10,3 (7,3-12,2)	9,6 (7,3-12,2)	April 2012 102 kg
γ %	13,6 (12-20)	-	9,7 (11-21)	11,8 (11,2-9,9)	10,7 (11,2-19,9)	Evolution of the tumour markers
A/G	1,6 (1,2-1,8)	-	1,9	1,88	-	NSE
IgG mg/dL	910 (700-1600)	-	705 (700- 1600)	-	-	November 2010 25 ng/mL
CaT mg/dL	9,1 (9-11)	-	9,2 (8,6-10,2)	-	-	February 2011 3.57 ng/mL
Ca ²⁺ mg/dL	4,14 (4,1-5,5)	-	4,04 (3,82- 4,82)	4,87 (4,20-5,20)	4,55 (4,20-5,20)	CEA
NSE ng/mL	25 ng/mL ($< 16,3$)	-	9,9 (< 17)	-	-	November 2010 7.72 ng/mL
CEA ng/mL	7,72 ng/mL ($< 4,3$)	-	3,57 ($< 4,3$)	-	-	February 2011 3.57 ng/mL

From an imaging and clinical point of view¹, starting from October 2010, we can identify three stages in the patient's evolution.

¹We shall follow the evolution of the second tumour relapse, as well as the patient's clinical evolution, based exclusively on the MRI scan reports and the assessment reports sent from Germany (to associate them with the lab test results, please see the Summarising Table)

1) Tumour remission during apitherapy (October 2010 – August 2011):

a) October 2010 to February 2011, when the KPS score increased from 40 to 70, the body weight dropped from 126 to 101 kg, proliferative mitosis was prohibited (the MRI scan conducted in December 2010) and the GBM went into remission (from the maximum spread recorded in October 2010, to the maximum remission in February 2011). The patient no longer suffered from epileptic seizures or from incontinence, he started recovering from a cognitive and sensory-motor viewpoint (from October 2010, during the first month of apitherapy). In February 2011, the tumour, which had reached its maximum remission stage, no longer showed its central necrosis area.

b) February to August 2011, when the body weight dropped to 75 kg. The patient was fully recovered from a cognitive and sensory-motor perspective², his KPS score being constantly assessed at 70³. The tumour evolves towards separating itself from the adjacent tissues and towards encapsulation. *At this point, in June 2011, the doctors at the German clinic talked to the patient and his family, about the possibility of a new operation*, after they had stated, since September 2010, that “we could not see” any efficient antineoplastic therapy option.

2) Tumour remission stability after apitherapy was ceased (August 2011 - April 2012)

The patient stopped coming to Romania and he gave up apitherapy in August 2011. We stopped receiving the assessment reports from the clinic in Germany. The stability of apitherapy effects during this period of time are proven only by the MRI scans Reports that we received. Until April 2012, they had constantly stated that *the glioblastoma remission was stabilised at the level reached in June 2011*.

3) Beginning of the third tumour relapse: the MRI scan conducted in April 2012 showed a recommencement of tumour invasiveness, the occurrence of small marginal necrosis areas and the re-occurrence of oedema. Another MRI scan conducted in September 2012 described the tumour evolution, which was very similar to the one recorded in September 2010, when the level of tumour invasiveness rendered any standard antineoplastic therapy impossible and inefficient and the patient’s clinical evolution was assessed at KPS 50.

In the absence of any medical documents after September 2012, we end our discussions about the patient’s evolution here. Shortly after September 2012, the outcome was fatal.

Conclusions

Standard GBM therapy - surgery, chemotherapy, radiotherapy and adjuvant medication – is approximately the same anywhere in the world. Differences may only occur in relation to the surgeon’s professionalism, to the chemotherapy substance used or the efficiency of the adjuvant medication.

Due to the blurry separation between the tumour and the surrounding tissues, the surgery conducted to eradicate the primary tumour usually has limited efficiency. As a rule, which was confirmed once again by the case presented here, chemotherapy, radiotherapy and the adjuvant medication cannot prevent tumour relapse. In this case, the first relapse occurred three years and three months after the surgery conducted for primary tumour. Surgery conducted to eradicate a relapsed tumour is always even less efficient than the initial surgery, undertaken for primary tumour.

The second tumour relapse usually occurs in a shorter period of time than the first one and the surgery, in this case, is less frequent. In the case presented here, the GBM relapse occurred one year and two months after the second surgery, which was conducted for the first relapse. One month later, the clinic admitted to have no efficient treatment left to use against the second tumour relapse: all standard intervention means had been exhausted. They did not prove to be very efficient and

²States that had been confirmed and re-confirmed by the assessment reports issued by the clinic in Germany. Despite that, however, in the absence of any other clinical observations, each assessment report stated that the patient was suffering from frontal syndrome. In reality, ever since February 2011, the frontal syndrome had become moderate and it was rarely showing any symptoms. It did re-occur, however, in March 2012, one month before the MRI scan discovered that the mitoses had been resumed, as well as the tumour progression (the third and final relapse).

³This is the constant KPS score recorded in the assessment reports issued in Germany. We think, however, that the patient’s positive evolution was actually the equivalent of KPS 80%, or at least close to it.

due, among other things, to the sheer aggressiveness of the therapy methods employed, the patient's clinical state became so bad that the therapy means could no longer be used.

Nevertheless, the standard glioblastoma therapy, from its diagnosis, can be considered a strategy that only postpones surrender. Not even the most reputed professionals can extend the limits of the therapeutic means they have at hand. The current medical theory regarding GBM, as well as the therapeutic methods available – cytostatic treatment, radiotherapy, adjuvant medication – seem to have become a sort of religion, with rigid rituals that are strictly known and applied by everybody, while waiting for a messianic cancer cure. It would be, however, difficult to find a religion that was not faced with heresies.

So, in this case, the heresy is us using apitherapy to treat GBM, while excluding any classic medication, relying exclusively on the therapeutic agents contained in the apitherapy products that we manufacture ourselves and being guided by our own theory related to this type of tumour! We, the heretics, do not ask anybody to believe without questioning. Nor are we interested in creating a so-called religion vs. heresy debate: standard medication vs. apitherapy. On the contrary, we hope that a “synod” of scholars (researchers, pharmacologists, clinical experts) would research the apitherapy domain and look for those agents that allowed a GBM patient with a KPS score of 40% that was deemed beyond redemption by the official religion, to be brought back to life and clinically elevated to a KPS score of 70, for an extended period of time.

This evolution recorded by our patient was a medical breakthrough, obtained using a unique theory and method, with therapeutic means also used for the first time. Theoretically, we regarded GBM as a disease characterised by immunosuppression, successor of an autoimmune dysproteinaemia. We did not make the proliferative glioblastoma our sole therapy target. On the contrary, we made efforts to restore physiological immunity, making the rebalanced body metabolism, an ally for our tumour-fighting therapy agents.

The tumour remission between October 2010 and February 2011, the remission stability maintained not only until the cease of therapy (June 2011) but also afterwards, until April 2012, prove not only the tumour-fighting potential of apitherapy products, but also the stability of their effects over time. The prohibition of mitosis, the tumour remission, the prohibition of neovascularisation, the extent of maximum tumour separation from the surrounding tissues, as well as the patient's clinical rehabilitation from KPS 40 to KPS 70 are, without any doubt, the effects of the apitherapy “heresy” and they were recorded in the assessment reports sent from Germany.

We cannot know, but can only assume how the glioblastoma might have evolved if the patient had continued his apitherapy. We don't know if the beginning of the relapse - the final relapse in April 2012 – could have been at least postponed, had the patient stuck to a well ordered lifestyle and a diet coordinated by us, even without apitherapy. It is possible that a new surgery would have had the best chances of success once the MRI scan showed a total “separation” of the tumour from its surrounding tissue.

Glioma prophylaxis in its benign stage

Any glioblastoma goes through an accumulation stage called glio-fibromatosis, when the glioma is formed. As a formation method, a benign glioma cannot be much different from the accumulation of fibrous proteins in areas other than the skull (for instance, a uterus fibroma or breast fibromas).

We think that the following factors facilitate the formation of benign gliomas:

- congenital inheritance of a maternal autoimmune dysproteinaemia (in the case presented above, the patient's mother had had a uterus fibroma surgically removed). Usually, children born from mothers who develop various forms of fibrous protein accumulations, inherit the mother's protein status: ALB drops towards or even below the normal value, while SPE shows an accumulation of globulin and fibrous proteins.
- congenital inheritance of maternal ionic hypocalcaemia or its later occurrence
- protein-rich diet (consisting of foods comprising an excess of amino-acids that are the globulin precursors, fibrous proteins and a deficit of amino-acids that are albumin precursors);

- fat-rich diet¹; dyslipidemia (either metabolic or by intake) leading to a fatty structure of the brain (generally present in cases of GBM);
- any other factors that lead to:
 - the proliferation of fibrosis globulins and the deterioration of A/G in favour of these globulins, with an increase of globulin γ towards or above the normal value threshold.
 - the ionisation of an ever smaller quantity of calcium, regardless of the CaT level (it is usually recorded around the minimum n.v. threshold but it can also reach higher values).

The most efficient prophylaxis of GBM occurrence consists of:

- maintaining a balanced TP, which is especially indicated by the balance of serum proteins (SP), monitored through serum protein electrophoresis (SPE), in such way to prevent the A/G ratio from dropping below 1.5 (provided that each globulin [α_1 , α_2 , β and γ] is within normal values); percentagewise, the more ALB drops below 60% of the total SP, the higher the risk of fibrous protein accumulation.
- rebalancing TP, by rebalancing the SP parameters indicated by SPE, if such parameters show any unbalance, but only before the start of glio-fibre proliferation.

The prophylaxis of glioma cancerization might be possible:

- If the benign glioma has started its formation but the cancerisation process had not begun yet, the restoration of TP balance, by rebalancing SP, shall stop the glioma's growth: the reduction of excess globulins up to their lowest limit will render their accumulation impossible and as a result, the existing glioma will stop growing.
- There might also be a chance of gradual glioma resorption², in which case, the proteins in its structure shall be reinserted in the normal flow of protein-fibre globulin metabolism, if a circulating deficit of such proteins can be triggered on purpose.
- Restoration of physiological glycaemia
- Simultaneous restoration of physiological lipidemia and even a long term hypolipidemia in the blood; such a state will lead to the fats in the brain being mobilised, transported by the blood and consumed to create energy (which is possible through severe limitation of food fats or by restoring the lipid metabolism in case of metabolic dyslipidemia).
- Restoring the physiological metabolism of calcium
- Prohibiting local angiogenesis; If neovascularisation has started, the resorption of newly-formed blood vessel through anti-angiogenic apitherapy (whose efficiency we have already proven) or through another anti-angiogenic medication which might be efficient.
- Surgery to remove the benign glioma, under the condition of protein normalisation, but only when the glioma's size becomes stable, when the glioma shows no vascularisation and it is clearly separated from the adjacent tissue, surgery is - or can be - free of any risk, including the risk of localised accumulation of glio-fibromas being resumed.

If TP, SPE, CaT and Ca^{2+} were among the routine lab tests, conducted periodically, the drop of albumin values and the increase of globulins, as well as the evolution towards ionic hypocalcaemia, might draw attention over the risk of fibrosis. If dyslipidemia and ionic hypocalcaemia become chronic, one can suspect a possible evolution towards the formation of a benign glioma.

¹Hyperlipidemia accompanied by dyslipidemia, is constantly present in the case of benign glioma formation and in the case of such glioma's cancerisation. Not all glioblastoma patients are obese – in some cases, metabolic dyslipidemia is also present, but the effects are the same.

²We can report no such case of a patient where a benign glioma stopped growing, nor can we report a case of resorption. We can, however, report cases of uterus fibromas that stopped growing and even started resorbing, as well as breast fibromas, liver fibrosis, lung interstitial fibrosis, etc. This is due, among other things, to the fact that gliomas are rarely diagnosed in their benign stage. And if they are discovered by imaging processes, classic medicine has no therapeutic protocol for this situation: Patients are only recommended to monitor the tumours by imagistic means (CT or MRI). Only patients who can no longer be helped by standard therapy, usually resort to our clinic, and thus, to apitherapy. By restoring the normal physiological protein levels, we think we can at least prohibit their growth and accumulation inside the glioma, if we can't do even more.

If fibrosis does not affect another organ, then it does not show on ultrasound and, in this case an MRI scan (rather than a CT) could reveal the occurrence of a glioma, even without suggestive symptoms. Now would be the time for the most successful prophylaxis intervention, meant to prevent its cancerization and to stop it from turning into GBM. A surgery is needed for its removal, but this surgery must not be the first medical action taken under any circumstance: surgical removal of the effect (the glioma) shall restore neither the protein metabolism nor the lipid, glycaemic or calcium metabolism, within normal physiological values. First, there must be a period of about 2-3 months, during which:

- the TP balance is restored, by rebalancing SP, in such way to ensure that the percentage level of ALB amounts to at least 60% of the total SP, with an A/G ratio of minimum 1.50, and only on the condition that each of the globulins alpha, beta and gamma, record values close to the average between the minimum and the maximum n.v. thresholds.

- metabolisms are restored, at systemic level, within normal physiological limits (proteins metabolism, lipid, carbohydrate, minerals, enzyme metabolism, etc.)

All these rebalancing efforts lead to a reduction of fibrosis globulin proteins circulating in the blood, to a level where they no longer have to be removed from the circuit and deposited in the glioma. In this situation, the benign tumour goes through an encapsulation process, which clearly separates it from its adjacent tissue.

There might be other therapies that can be used to obtain the same results but to us, apitherapy is the most efficient intervention mean, thanks to its results obtained by rebalancing the physiological metabolism. The encapsulation of the benign tumour provides the perfect timing for glioma resection, with two huge advantages: injury of adjacent tissue is prevented and, because its glial cell "supply channels" have been cut off, the glioma can be completely removed, without the risk of a later relapse.

Apitherapy can make the surgery for glioblastoma multiforme more efficient

We have strong reasons to state that apitherapy should be applied before surgery, in cases where the glioma has already been through the cancerization process and has become an invasive glioblastoma. One of the arguments for this statement is the very case we described above. Apitherapy prohibited the mitosis and led to tumour remission when standard therapy had admitted its inefficiency. This evolution took place after the second tumour relapse, whose invasive and disabling progression ran out of control.

If apitherapy had been used before surgery conducted for the primary tumour, it might have led to a better differentiation of the tumour from its adjacent tissues, through its proven antiangiogenic, antimitotic, and anti-immunosuppressant (immunomodulatory) effects.

Given the fact that apitherapy prohibited mitosis and forced the tumour into remission after its second relapse when the patient's para-clinical state was deemed as hopeless, we believe that it would have generated at least equally efficient results, had it been applied before the first surgery. A first surgery conducted on a well differentiated glioblastoma whose mitosis had been prohibited could be a unique chance for both the surgeon and the patient.

We also bring another argument: *the case of a 66 year old female patient, 1.60 m, 45 kg, who underwent surgery for a primary tumour - GBM - on 31.08.2013.* She followed the same standard therapy path as the patient presented above: Temodal, radiotherapy, (60 Gy), adjuvant medication. From a para-clinical point of view, her state of immunosuppression, hyperglycaemia (of metabolic origin, in this case), etc, was identical to the one encountered in the case described above. Two main differences were the age and the existence of chronic dysproteinaemia, accompanied by a drop of ALB and an abnormal increase of protein-fibre globulins: 25 years prior to this disease, the patient had been through a complete hysterectomy due to a uterus fibroma. Therefore, her tendency towards fibrosis hyperglobulinemia was chronic and the possibility of TP rebalance, based on the information provided by SPE, was neglected.

On 19.11.2013, during a re-assessment, a CT head scan – native and with contrast agent – showed the occurrence of a GBM relapse. So, in this case, the tumour relapse occurred less than two and a half months after the primary tumour surgery.

On 10.12.2013 the patient started apitherapy. Her clinical state was similar to the one encountered in the patient coming from Germany, the only difference being the fact that this patient also suffered from hemiparesis and she could only walk if assisted. In this case the Methylprednisolone corticosteroid was represented by Dexamethasone. From the very first month of apitherapy, her clinical state improved dramatically.

During a new reassessment conducted in February 2014, after two months of apitherapy, the CT scan showed a cystic frontal mass measuring 5/5 cm “that could be compared to a tumour relapse surrounded by a peritumoral oedema” with a positive evolution and a significant neurological improvement. It was obvious that the GBM relapse was no longer progressing.

During a new reassessment, made on 12.09.2014, after nine months of apitherapy, the CT scan “shows a frontal contrast plug area, placed parasagittal, on the left side, ***which would suggest a small tumour relapse.*** There is no mass effect or median line movement. Under conventional treatment... positive evolution with a significant neurological improvement. No neurosurgical indication at this time.”

If the doctor in the German clinic was informed of the apitherapeutic treatment conducted in Romania and the exclusion of the recommended medication, the second patient, in Romania did not have the courage to inform her doctor that she had ceased standard therapy (with Temodal and adjuvant medication) and that the positive evolution was due only to apitherapy. Thus the doctor believes that the positive evolution was recorded “under standard treatment”, as stated by the assessment reports.

Therefore, if the first relapse occurred less than two and a half months after the primary tumour surgery, with a clear worsening of the patient’s clinical state, after two months of apitherapy¹, the relapsed tumour was obviously in remission and the mitosis was prohibited.

We think that these evolutions – both of the first patient and that recorded in this second case, which was summarily described here – would have been different had apitherapy been used prior to initial surgery. Perhaps some clinic in Germany or in some other country will be interested in apitherapy applied prior to standard therapy in glioblastoma multiforme treatment, at least at clinical research level. In Romania, such a heresy is clearly excommunicated!

¹The case documentation is available under the reference: R30/104 – B 29 in the Apitherapy Medical Center’s database.