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CLINICAL STUDY

Compassionate use of Quantum Magnetic Resonance Therapy for treatment of children with Diffuse Brainstem Glioma in Mexico City: a single institutional experience

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Abstract

Purpose Diffuse Brainstem Glioma (DBG) is a catastrophic brain tumor with a survival rate of less than 10% two years after diagnosis despite the existence of different treatment protocols. Among the devices that use magnetic fields generated by Magnetic Resonance Imaging is Quantum Magnetic Resonance Therapy (QMRT).

Methods Five children diagnosed with DBG in our institution in Mexico City underwent treatment of compassionate use with QMRT between December 2018 and July 2019. A survival analysis was performed with previously reported historical data (n = 15).

Results Two patients (40%) survived after three years of follow-up; the log-rank test showed a statistically significant difference in overall survival between both groups ($p = 0.032$). All patients tolerated the treatment adequately without reporting any severe clinical or neuroradiological adverse effects. Of the patients included, all showed a decrease in the tumor one month after the end of the treatment, although there was great variability in the response and the difference was not statistically significant ($p = 0.06$).

Conclusions Although future investigations are needed to confirm the findings reported in the present study, the improvement in survival is promising for a group of patients whose prognosis has been catastrophic over the years.

Trial registration NCT03577600.

Keywords Pediatric brain tumor · Diffuse midline glioma · Diffuse intrinsic pontine glioma · Brainstem tumors · Magnetic field therapy · Quantum magnetic resonance therapy

Introduction

Diffuse Brainstem Glioma (DBG) represents 10–15% of brain tumors and 80% of brainstem tumors [1, 2]. In the United States, DBG is diagnosed in approximately 300 children yearly, with a median age of diagnosis between 6 and 7 years [3]. Despite advances in the management of central nervous system neoplasms, DBG persists as a devastating glial tumor with less than 10% of patients surviving beyond 2 years from diagnosis [4]. At our Institution, the Hospital Infantil de México Federico Gómez, we reported a median survival time of 7 months (IQR: 5.0–8.5), with none of the patients surviving beyond 2 years [5].

The physical fields generated by magnetic resonance imaging have been extensively studied in different modalities to carry out therapeutic actions that have shown promising results which indicate it to be safe as a therapeutic agent [6]. One of these modalities is Quantum Magnetic Resonance Therapy (QMRT), also known as CYTOTRON®, in which poly-dimensional, rotating target-specific, modulated radio frequencies are delivered in the presence of an instantaneous magnetic field (U.S. Patent 9,162,076 B2 awarded 20/10

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2015, European Patent EP 175,350,831, awarded 3/11/2015, Chinese Patent issued 2010, 09/08) [7].

There is evidence that of low intensity, intermediate frequency, electric fields inhibit cancerous cell growth in vitro in brain tumors by an anti-microtubule mechanism of action, [8]. In the only published clinical trial of a sample of adult patients (n = 86) that completed the treatment with QMRT, 42% (n = 36) had no interval change in tumor characteristic after one month [7]. No data is provided about the ages and characteristics of the 13 patients that were included with brain tumors or if they were part of the group that responded. However, during therapy or in the follow up period no adverse event or adverse device effect severe enough-either superficial or systemic -to prompt therapy termination, were reported [7].

The devastating clinical course present in DBG patients makes them candidates for compassionate use of experimental treatments such as QMRT despite the existence of conventional treatment [9]. QMRT has shown promising data in solid tumors in the adult population and with an adequate level of safety [7]. This report describes the compassionate use of QMRT for children diagnosed with DBG in our institution in Mexico City.

Methods

Between December 2018 and July 2019, five patients with a diagnosis of DBG by Magnetic Resonance Imaging were recruited as part of the compassionate use of QMRT in patients with brain tumors at our institution in Mexico City, Mexico (ClinicalTrials.gov: NCT03577600). The patients were subsequently registered until July 2021 and compared with previously published historical data of 15 patients with DBG diagnosed between January 2008 and December 2012 [5]. The same radiological diagnosis criteria was used for the control and QMRT group, none of them had a surgical procedure for biopsy as is not a standard procedure in our Institution. All included patients received the standard conventional treatment with radiotherapy and temozolomide with no additional experimental medical therapies. None of the patients had any specific genetic syndrome. Prediagnostic symptomatic interval was measured from the symptom onset to the neuroradiological confirmation, pre treatment interval from the radiological diagnosis to the initiation of the first conventional treatment and overall survival from the time of the neuroradiological diagnosis. The QMRT treatment interval was measured from the last dose of radiotherapy. Before entering the present study, they were evaluated by the neurosurgery, radiotherapy and oncology services and were considered candidates for compassionate use. All included patients presented clinical progression defined as a persistent decrease in the Lansky Performance Scale in the last two months.

All guardians or legal guardians, as well as patients, if applicable, signed the informed consent and assent form in accordance with international ethical standards and those established within our Institution. The protocol used was a daily treatment of one hour a day for 28 days without interruption with QMRT without sedation. The details of the procedure can be seen in Kumar, R., et al. [7], using radiofrequency in degenerative ranges directly targeting the tumor.

Survival was measured from the radiological diagnosis of DBG. A control brain Magnetic Resonance Imaging (MRI) was performed one week before treatment and one and twelve months after the application of the treatment. Lansky Performance Scale was measured with every MRI. An independent neuroradiologist performed the tumor measurements using the technique described by Richtig, E., et al. [10], before and after the treatment. Statistical analysis was performed using R (version 4.0.4) [11] and RStudio (Version 1.4.1106) [12] with the packages 'survival' version 3.2–7 [13] and 'survminer' version 0.4.9 [14]. Survival time was used as a measure of comparison. The survival rate was calculated using the Kaplan–Meier estimates and the log-rank test was used to compare the survival of different groups. The paired-sample Wilcoxon signed-rank tests were used to compare the volume before and one month after treatment. A p values of less than 0.05 were considered to indicate a significant difference.

Results

Five patients met the inclusion criteria. The characteristics of these patients, as well as the historical control group are shown in Table 1. The median age at diagnosis of the group treated with QMRT was 5 years (IQR: 4–7). The pre

Table 1 Summary of patients

	Type of Treatment	
	QMRT	Control
N	5	15
Sex = Male (%)	3 (60.0)	9 (60.0)
Age (median [IQR])	5.00 [4.00, 7.00]	6.00 [5.00, 7.00]
Survival time (median [IQR])	22.00 [11.00, 30.00]	7.00 [5.00, 8.50]
Deceased (%)	3 (60.0)	12 (80.0)
Prediagnostic symptomatic interval [months] (median [IQR])	4.00 [3.00, 5.00]	4.00 [2.00, 5.00]
QMRT treatment interval (median [IQR])	3.00 [2.00, 3.00]	0.00 [0.00, 0.00]

treatment interval median for the first conventional treatment for the QMRT group was 10 days (IQR: 5–20) and 12 (IQR; 9–20) for the historical control. The median time since the last radiotherapy session before the compassionate use was 3 months (IQR: 2–3). All patients tolerated the treatment adequately without reporting any severe clinical or neuroradiological adverse effects. During the cycle, within the next hour of application of the treatment and in no more than 50% of sessions, three reported sensation of thirst, two mild headaches, one generalized paresthesia, and one mild dizziness. No adverse effects required intervention and were resolved upon treatment completion. The mean survival of the group treated with QMRT was 22 months [IQR: 11–30] and of the historical controls, it was the previously reported 7 months (IQR: 5–8.5). The survival group did not receive any additional treatment during the follow up.

The Kaplan–Meier curve with its corresponding survival table for the two groups is shown in Fig. 1. None of the historical controls had survived (n = 15), while those treated with QMRT (n = 5) had 40% remained alive two years after diagnosis (n = 2), an effect that has been maintained three years after the onset of treatment. The log-rank test showed a statistically significant difference in overall survival between both groups ($p = 0.032$). Of the patients included, all showed a decrease in the tumor one month after the end of the treatment, although there was great variability in the response and the difference was not statistically significant ($p = 0.06$). Individual values are shown in Table 2 and their images in Fig. 2.

Discussion

Despite the use of various treatment strategies both conventional and experimental, the prognosis of DBG patients has not improved in at least three decades [1, 15]. Regardless of the efforts made with different therapeutic modalities over the years, less than 10% of patients survive two years after their diagnosis [4, 16]. The improvement in survival in the population studied in our report represents an advance compared to those reported with other treatment schemes [17].

The therapeutic use of electromagnetic fields for the treatment of cancer is an active area of research that has yielded promising results in tissue, animal, and clinical studies, leaving behind the initial controversies and skepticism [18, 19]. Among the evidence in animal studies, it is considered their ability to inhibit tumor growth by the effect caused by the iron molecules that control the folding of p53 and the binding activities to DNA [20]. This is one of the possibilities that explains the reason for the

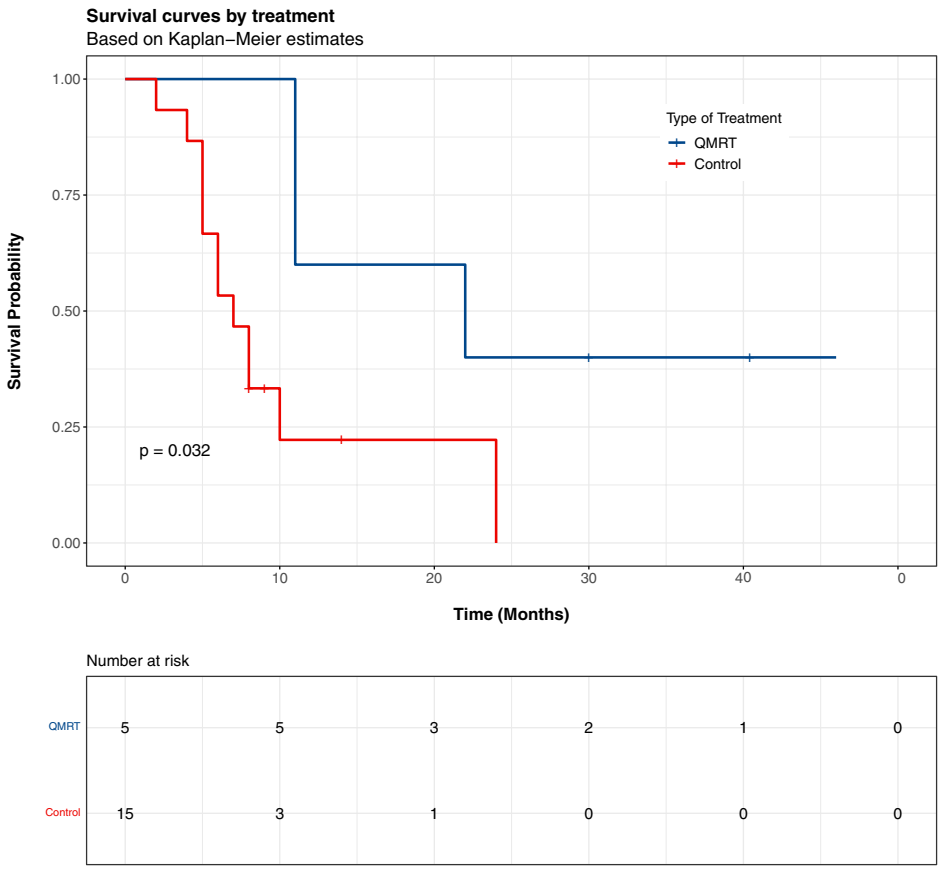

Fig. 1 Kaplan Meier survival curve and table by treatment group

Table 2 Individual characteristic of QMRT group

ID	Sex	Age (years)	Deceased	Survival Time (months)	Vol* t0 (cm)	Vol* t1 (cm)	Vol* t2 (cm)	LPS+ t0	LPS+ t1	LPS+ t2
A	Male	8	No	46	8.4862	6.8116	5.96	40	70	90
B	Female	3	Yes	11	29.98	28.46	–	40	60	–
C	Male	7	Yes	22	60.4224	48.4667	–	30	70	–
D	Male	4	Yes	11	30.7917	23.769	–	30	60	–
E	Female	5	No	30	7.9661	5.6183	3.08	40	60	80

t0 = one week before first session of treatment

t1 = one month after final session of treatment

t2 = twelve month after final session of treatment

*Volume

+Lansky Perfomance Scale

improvement observed in our group of patients, with the important advantage of not provoking significant adverse effects or secondary injuries. Another explanation could be an indirect effect in the microglia surrounding the tumor [21], an effect that has been demonstrated also in animal models [22].

The use of QMRT in adults with solid tumors has previously been shown to be a viable palliative treatment option [7], and it is unrelated to other pseudo therapies that have used the same term [23]. Their classification among magnetic field-based therapeutic modalities [24] is still open to debate [6]. We considered that the choice of the word "quantum" is not justified by the inventors and is a term that causes confusion in the scientific community. Efforts should be expanded in search of concrete data that demonstrates its true mechanism of action, beyond the theoretical framework that led to its invention. Leaving aside these controversial points, the results of the present investigation with a three-year follow-up allowed us to establish that QMRT prolongs overall survival in a statistically significant way ($p = 0.032$) in patients with DBG. These results are promising when we compare them to those previously reported using other treatments [25].

Among the limitations of the current study is the need to increase the number of patients in the treatment cohort to verify the promising results obtained in our sample. Future research should contemplate measurement of other clinical variables such as functionality, quality of life as well the development of measurement scales such as clinical scores specific to DBG that would allow us to better evaluate the clinical response of patients to treatment [26]. Analysis of biopsy material could also help to determine if there are molecular differences between the tumor types; this could help better understand mechanisms behind the heterogeneous response of our sample group [27, 28]. Biological variability in the type of tumor could explain the positive response in a subgroup of DBG patients, but this invasive procedure is not yet part of the standard care procedures in our institution, since as to this day it has no clinical implications for the therapeutic decisions or the survival of the patients.

It is clear to us that more research is needed to establish the use of the QRMT as a compassionate treatment for solid brain tumors and its future as an adjuvant in their treatment. However, the experience acquired during this study is, to our knowledge, the first clinical report that demonstrates its efficacy in improving survival in pediatric patients with brain tumors in which the different therapeutic modalities have not helped to improve their survival. Despite these encouraging results, the research did not continue for reasons related to the conclusion of the agreement for the use of QMRT in our institution.

Conclusion

QMRT was well tolerated in our series of pediatric patients with DBG, and there was a statistically significant increase in overall survival ($p = 0.032$) when using historical controls. The mean survival of the group treated with QMRT was 22 months [IQR: 11–30] and that of the controls was 7 months (IQR: 5–8.5). Although future investigations need to confirm the findings reported in the present study, the improvement in survival is promising for a group of patients whose prognosis has been catastrophic over the years.

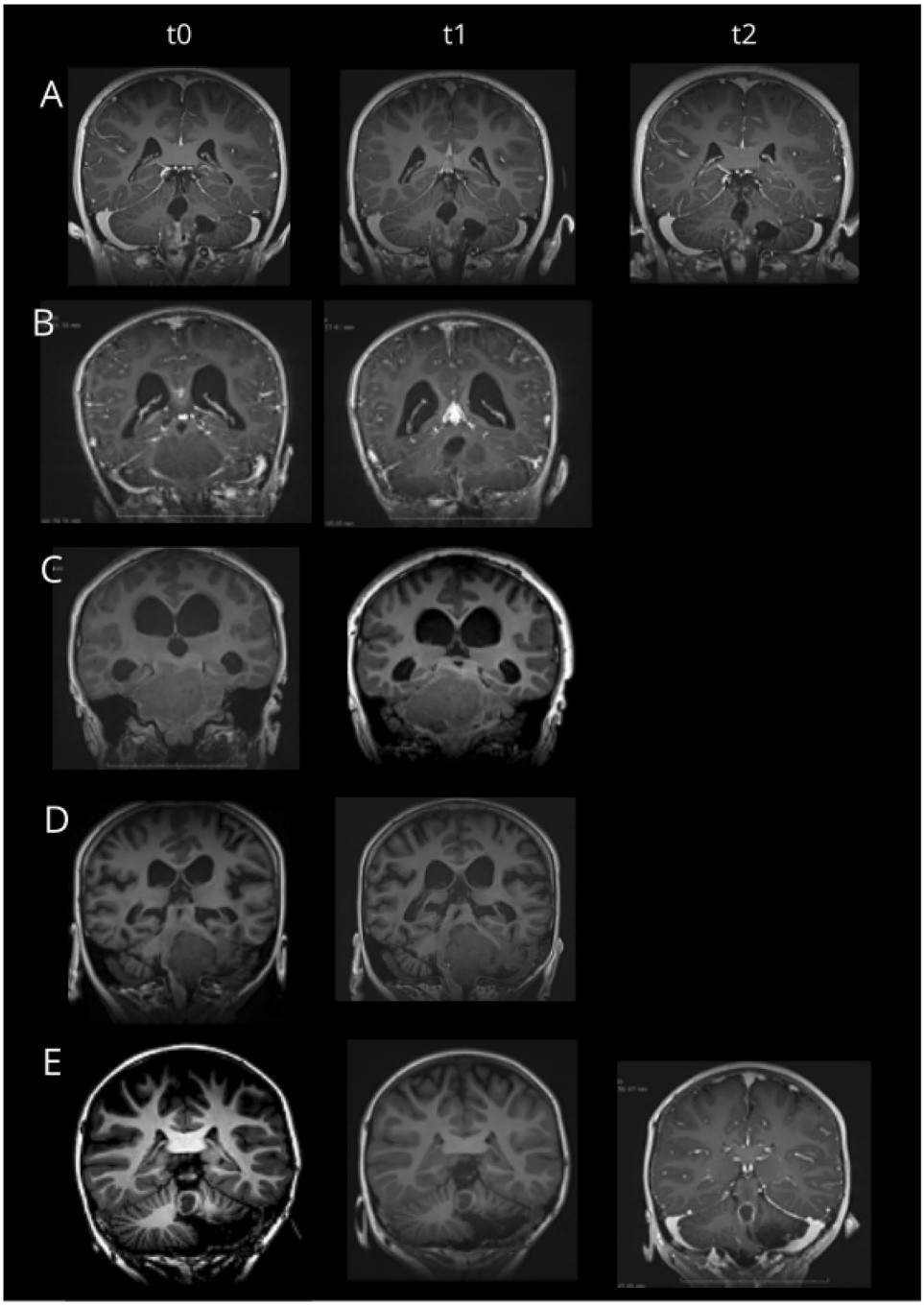

Fig. 2 T1 Magnetic resonance imaging of all patients, rows from A to E show the individual ID and columns the time when it was taken

Author contributions All authors contributed to the study conception and design. Material preparation and data collection were performed by EJBP, PDS, SHT and JCGB. Analysis was performed by DEAA and JCGB. The first draft of the manuscript was written by DEAA and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors declare that they have no potential conflicts of interest. There is no financial interest or benefit to disclose.

Ethical approval The study was approved by an Internal Institutional Review Board.

References

1. Jansen MHA, van Vuurden DG, Vandertop WP, Kaspers GJL (2012) Diffuse intrinsic pontine gliomas: a systematic update on clinical trials and biology. Cancer Treat Rev 38:27–35
2. Noureldine MHA, Shimony N, Jallo GI (2020) Diffuse Midline Glioma – Diffuse Intrinsic Pontine Glioma. In: Jallo GI, Noureldine MHA, Shimony N (eds) Brainstem Tumors: Diagnosis and Management. Springer International Publishing, Cham, pp 159–193
3. Monje M, Mitra SS, Freret ME, Raveh TB, Kim J, Masek M et al (2011) Hedgehog-responsive candidate cell of origin for diffuse intrinsic pontine glioma. Proc Natl Acad Sci U S A 108:4453–4458
4. Hargrave D, Bartels U, Bouffet E (2006) Diffuse brainstem glioma in children: critical review of clinical trials. Lancet Oncol 7:241–248
5. Barragán-Pérez EJ, Altamirano-Vergara CE, Alvarez-Amado DE, García-Beristain JC, Chico-Ponce-de-León F, González-Carranza V et al (2020) The role of time as a prognostic factor in pediatric brain tumors: a multivariate survival analysis. Pathol Oncol Res 26:2693–2701
6. Bogachev YV, Nikitina AV, Frolov VV, Chizhik VI (2020) MRI-Guided Therapy Tech Phys 65:1427–1435
7. Kumar R, Vijay KR (2016) Quantum magnetic resonance therapy: Targeting biophysical cancer vulnerabilities to effectively treat and palliate. J Clin Exp Oncol. https://doi.org/10.4172/2324-9110.1000156
8. Kirson ED, Dbalý V, Tovarys F, Vymazal J, Soustiel JF, Itzhaki A et al (2007) Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors. Proc Natl Acad Sci U S A 104:10152–10157
9. Caplan AL, Ray A (2016) The ethical challenges of compassionate use. JAMA 315:979–980
10. Richtig E, Langmann G, Müllner K, Richtig G, Smolle J (2004) Calculated tumour volume as a prognostic parameter for survival in choroidal melanomas. Eye 18:619–623
11. Core Team R, Others. R: a language and environment for statistical computing. R Foundation for statistical computing, Vienna. 2013.
12. Team R, Others. RStudio: integrated development for R. RStudio, Inc, Boston, MA. 2015;42: 14.
13. Therneau TM, Lumley T. Package "survival." Survival analysis Published on CRAN. 2014.
14. Kassambara A, Kosinski M, Biecek P, Fabian S. Package "survminer." 2017.
15. Robison NJ, Kieran MW (2014) Diffuse intrinsic pontine glioma: a reassessment. J Neurooncol 119:7–15
16. Glod J, Rahme GJ, Kaur H, Raabe EH, Hwang EI, Israel MA (2016) Pediatric brain tumors: current knowledge and therapeutic opportunities. J Pediatr Hematol Oncol 38:249–260
17. Hassan H, Pinches A, Picton SV, Phillips RS (2017) Survival rates and prognostic predictors of high grade brain stem gliomas in childhood: a systematic review and meta-analysis. J Neurooncol 135:13–20
18. Macklis RM (1993) Magnetic healing, quackery, and the debate about the health effects of electromagnetic fields. Ann Intern Med 118:376–383
19. Basford JR (2001) A historical perspective of the popular use of electric and magnetic therapy. Arch Phys Med Rehabil 82:1261–1269
20. Tofani S, Cintorino M, Barone D, Berardelli M, De Santi MM, Ferrara A et al (2002) Increased mouse survival, tumor growth inhibition and decreased immunoreactive p53 after exposure to magnetic fields. Bioelectromagnetics 23:230–238
21. Badie B, Schartner J (2001) Role of microglia in glioma biology. Microsc Res Tech 54:106–113
22. Yamaguchi S, Ogiue-Ikeda M, Sekino M, Ueno S (2006) Effects of pulsed magnetic stimulation on tumor development and immune functions in mice. Bioelectromagnetics 27:64–72
23. Hornberger J (2019) Who is the fake one now? Questions of quackery, worldliness and legitimacy. Crit Public Health 29:484–493
24. Markov MS (2007) Magnetic field therapy: a review. Electromagn Biol Med 26:1–23
25. Rashed WM, Maher E, Adel M, Saber O, Zaghloul MS (2019) Pediatric diffuse intrinsic pontine glioma: where do we stand? Cancer Metastasis Rev 38:759–770
26. Hollingworth MA, Zacharoulis S (2020) Development of a clinical scale for assessment of patients with diffuse intrinsic pontine glioma (DIPG) receiving experimental therapy: the PONScore. J Neurooncol 149:263–272
27. Leach PA, Estlin EJ, Coope DJ, Thorne JA, Kamaly-Asl ID (2008) Diffuse brainstem gliomas in children: should we or shouldn't we biopsy? Br J Neurosurg 22:619–624
28. Manjunath N, Jha P, Singh J, Raheja A, Kaur K, Suri A et al (2021) Clinico-pathological and molecular characterization of diffuse midline gliomas: is there a prognostic significance? Neurol Sci 42:925–934