ScientificScholar®
Knowledge is power
Publisher of Scientific Journals

www.surgicalneurologyint.com

Surgical Neurology International

Editor-in-Chief: Nancy E. Epstein, MD, Professor of Clinical Neurosurgery, School of Medicine, State U. of NY at Stony Brook.

SNI: Neuropsychiatry

Editor
Miguel Faria, MD
President, Hacienda Publishing, Inc., USA

SNI
Open Access

Case Report

Bilateral hypothalamotomy plus dominant amygdalotomy with Gamma Knife radiosurgery. A non-invasive alternative when everything has failed in the management of aggressive behavior disorder

Oscar I. Molina Romero[1,2], Juan Carlos Diez-Palma[1], Andrés Fonnegra-Caballero[1], Andrés Segura-Hernández[1], Roberto Matinez-Alvarez[3], Edgar Yamhure[4], Julian Felipe Camargo[2], Julio Roberto Fonnegra-Pardo[1]

[1]Department of Neurosurgery, Fundación Clínica Shaio, [2]Neurosurgery Program, Universidad El Bosque, Bogotá, Colombia, [3]Department of Neurosurgery and Gamma Knife Radiosurgery, Hospital Ruber Internacional, Madrid, Spain, [4]Department of Psychiatry, Instituto Colombiano del Sistema Nervioso - Clínica Monserrat, Bogotá, Colombia.

E-mail: *Oscar I. Molina Romero - oscarmolinaromero1@gmail.com; Juan Carlos Diez-Palma - jdiezpalma@yahoo.es; Andrés Fonnegra-Caballero - andres.fonnegra@neuroplan.co; Andrés Segura-Hernández - andres.seguramd@gmail.com; Roberto Matinez-Alvarez - rob.martinez@telefonica.net; Edgar Yamhure - eyamhure@hotmail.com; Julian Felipe Camargo - juliancamargoch@gmail.com; Julio Roberto Fonnegra-Pardo - juliofonnegra@icloud.com

***Corresponding author:**
Oscar I. Molina Romero,
Department of Neurosurgery,
Fundación Clínica Shaio,
Bogotá, Colombia.

oscarmolinaromero1@gmail.com

Received: 12 October 2024
Accepted: 23 November 2024
Published: 20 December 2024

DOI
10.25259/SNI_860_2024

Quick Response Code:

ABSTRACT

Background: Impulsive aggression is the core symptom of intermittent explosive disorder, which can be a feature of several psychiatric disorders. There is a subset of individuals who do not respond adequately to medical treatment; they are treatment refractory. The objective of this report is to describe a case of a patient with a background of schizophrenia and concomitant refractory aggressiveness disorder, treated with two-stage bilateral hypothalamotomy and unilateral amygdalotomy with Gamma Knife radiosurgery (GKR).

Case Description: A 36-year-old male presented with a background of paranoid schizophrenia. Episodes of self- and hetero-aggressiveness were present at the initial diagnosis. High dosages of psychotropic medication were taken, and 70 sessions of electroconvulsive therapy were performed; however, no adequate response was obtained. Bilateral hypothalamotomy plus left amygdalotomy through GKR was performed. After 25 months of follow-up, a marked decrease in the frequency, degree, severity of aggressiveness and the requirement for psychotropic medications was observed.

Conclusion: Hypothalamotomy plus amygdalotomy with Gamma Knife may be an effective ablative technique for the management of refractory aggressive disorder in patients with mental illness.

Keywords: Aggressive behavior disorder, Amygdalotomy, Gamma Knife radiosurgery, Hypothalamotomy, Stereotactic radiosurgery

INTRODUCTION

Impulsive aggression is the core symptom of intermittent explosive disorder, which is characterized by episodes of disproportionate physical or verbal attacks without clear triggers and with a deliberate intention of destruction.[11] Often, this type of aggression is associated with high levels of

autonomic arousal and impulsivity,[22] which can be a feature of several psychiatric disorders, including schizophrenia, some personality disorders, autism spectrum disorder, post-traumatic stress disorder, and bipolar disorder.[2]

Despite the variety of drugs and doses used to treat aggression, there is a subset of individuals who do not respond adequately to medical treatment; they are treatment refractory. Surgical interventions targeting the amygdala or hypothalamus have been proposed for this limited population. Exploring non-invasive alternatives in managing this pathology is important to achieve adequate control and reduction of the disease burden while reducing the risk of complications associated with the procedure.

The objective of this report is to describe a case of a patient with a background of schizophrenia and concomitant refractory aggressiveness disorder, treated with two-stage bilateral hypothalamotomy and unilateral amygdalotomy with Gamma Knife radiosurgery (GKR).

CASE PRESENTATION

A 36-year-old male bachelor with no background of psychoactive substance use or alcoholism was diagnosed at age 21 with visual and auditory hallucinations. Paranoid schizophrenia was considered. In addition, episodes of self- and hetero-aggressiveness were present from the initial diagnosis, triggering, among other injuries, repeated craniofacial trauma and a serious open wound on his hand.

He took levomepromazine 250 mg/day, clozapine 1300 mg/day, and clonazepam 2 mg every 12 h. In addition, 70 sessions of electroconvulsive therapy were performed; however, no adequate response was obtained, and prolonged periods of hospitalization in the psychiatric unit were required.

The case was discussed on an interdisciplinary medical board with psychiatry and neurosurgery. Bilateral hypothalamotomy plus left amygdalotomy through GKR was proposed [Figure 1]. Before the procedure, informed consent was obtained as well as approval from the institutional ethics committee (DIB 43–4) was required for this report. Two-stage management was decided; each one was performed under general anesthesia and local anesthesia for fixation of the stereotactic frame. The location of the therapeutic targets and planning of the radiation dosage were carried out through the Leksell Gamma Plan program.

In the first stage, the selected targets were the left posteromedial hypothalamus and the central nucleus of the left amygdala. The posteromedial hypothalamus was located 3 mm behind the mid-commissural point, 5 mm below the mid-commissural point, and 2 mm lateral to the midline. One shot with a 4 mm collimator was used with a maximum dose of 125 Gy and isodose of 50%. The central nucleus of the left amygdala was located under direct vision in magnetic resonance imaging. One shot with a 4 mm collimator was used with a maximum dose of 120 Gy and isodose of 50%. The duration of this first session was 140 min. After 10 months, a second stage treatment was performed where the right posteromedial hypothalamus was treated using the same dosage and coordinates as the contralateral hypothalamus. The duration of this session was 140 min.

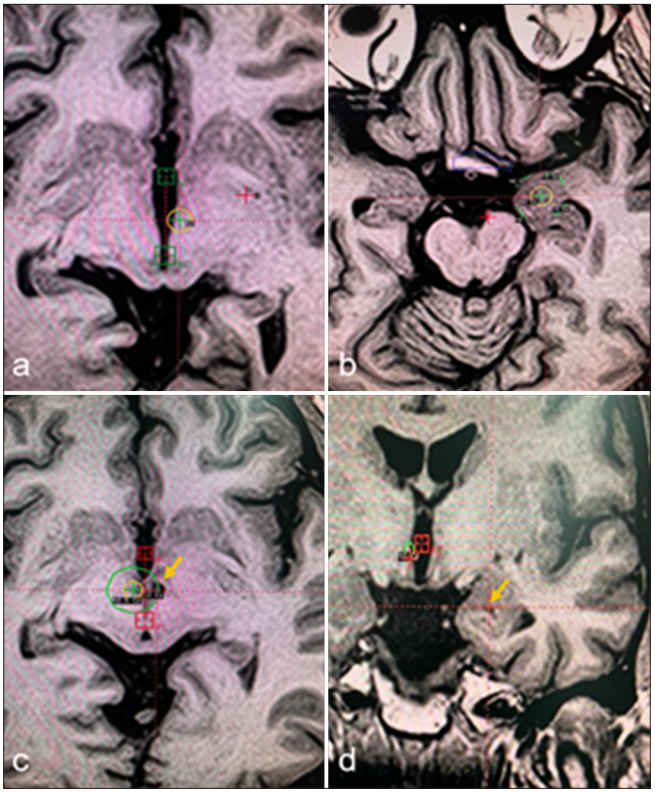

Figure 1: T1-weighted MRI shows the planning of the two-stage treatment with GKR. a) Axial slide showing the prescription dose (62.5 Gy) (yellow circle and green cross) at the level of the left posteromedial hypothalamus. The upper green box represents the anterior limit of the inter-commissural line (AC) and the lower one, the posterior limit (PC). The red plus depicts the amygdala treatment level located at lower levels in the axial plane. b) Axial slide showing the prescription dose of the central nucleus of the left amygdala (60 Gy) (yellow circle and green cross), and the safety dose (10 Gy) represented by the green circle. The red plus depicts the hypothalamus treatment level located at upper levels in the axial plane Ten months after the first treatment, a new MRI was performed to plan the second session. c) Axial slide displays the coverage dose of the right posteromedial hypothalamus (62.5 Gy) (yellow circle), with the safety dose (10 Gy) (green circle), and ablative changes at the level of the left posteromedial hypothalamus (yellow arrow). The upper red box symbolizes the anterior limit of the inter-commissural line (AC) and the lower one, the posterior limit (PC). d) Coronal slide demonstrates an ablative effect at the level of the central nucleus of the left amygdala (yellow arrow) as well as the anteroposterior projection of the inter-commissural line (red box). AC: Anterior commissure, PC: Posterior commissure

For clinical follow-up, 3 scales were used: (1) Modified overt aggression scale,[16] composed of 5 categories (verbal aggression, aggression against property, auto aggression, and physical aggression) with a range score from 0 to 40 points, being a higher score, a greater degree of aggressiveness; (2) Aggressive Behavior Scale,[18] which classify the frequency and severity of aggressiveness into 4 categories: None: 0, moderate: 1–2, severe: 3–5, very severe: 6–12 points; and (3) Global Assessment of Functioning,[1] which evaluates the functioning of patients with mental illness with a score from 0 to 100, being 100 points the highest degree of functionality.

After 25 months of follow-up, a marked decrease in the frequency, degree, and severity of aggressiveness was observed [Table 1]. In addition, a considerable improvement in the patient's functional status was achieved, and the requirement for psychotropic medications decreased (levomepromazine 100 mg/day, Clozapine 400 mg/day, and clonazepam 3 mg/day). This improvement occurred progressively, being approximately 50% before the second stage of treatment. There were no immediate or chronic complications attributable to the treatment.

DISCUSSION

Mental illnesses are a leading cause of disability worldwide. Specifically, schizophrenia is a chronic and severe mental illness affecting 20 million people worldwide.[7] Individuals

Table 1: Shows the results of 3 clinical scales used for patient follow-up. The evolution of the intensity and frequency of aggressive symptoms and functional capacity was evaluated. The results are described in 3 moments: (1) before the first stage treatment with Gamma Knife (Before 1° GKR); (2) before the second stage treatment with Gamma Knife (Before 1° GKR); and (3) at the time of the last follow-up, 25 months after the beginning of treatment with Gamma Knife radiosurgery (follow-up).

Modified overt aggression scale							
Category	**Score**			**Weights**	**Weighted sum**		
	Before 1° GKR	**Before 2° GKR**	**Follow-up**		**Before 1° GKR**	**Before 2° GKR**	**Follow-up**
Verbal aggression	3	1	0	X1	3	1	0
Aggression against Property	3	2	0	X2	6	4	0
Autoaggression	4	2	0	X3	12	6	0
Physical aggression	3	1	0	X4	12	4	0
Total Weighted Score					33	15	0

Aggressive Behavior Scale			
Item	**Before 1° GKR**	**Before 2° GKR**	**Follow-up**
Verbally Abusive	2	1	0
Physically Abusive	2	1	0
Socially Inappropriate/ Disruptive Behaviour	1	0	0
Resists Care	3	1	0
Total	8	3	0

Global assessment of functioning			
	Before 1° GKR	**Before 2° GKR**	**Follow-up**
Score	15	60	70
Description	Some danger of hurting self or others (e.g., suicide attempts without clear expectation of death; frequently violent; manic excitement) OR occasionally fails to maintain minimal personal hygiene (e.g., smears feces) OR gross impairment in communication (e.g., largely incoherent or mute)	Moderate symptoms (e.g., flat affect and circumstantial speech, occasional panic attacks) OR moderate difficulty in social, occupational, or school functioning (e.g., few friends, conflicts with peers or co-workers)	Some mild symptoms (e.g., depressed mood and mild insomnia) OR some difficulty in social, occupational, or school functioning (e.g., occasional truancy or theft within the household), but generally functioning pretty well, has some meaningful interpersonal relationships

GKR: Gamma knife radiosurgery

with schizophrenia or other psychosis have a higher rate of aggressive behavior, which can be 4–6 times higher than the general population, regardless of the concomitant use of psychoactive substances.[5]

The consequences of violent manifestations in the population with mental illness can be significant not only for patients but also for their immediate community. These generate a high economic and disease burden and also increase the social stigma around people with mental illness.[21] It has been found that patients with schizophrenia and aggression disorder were significantly employed less, experienced more lifetime hospitalization episodes, reported taking more psychotropic medication, and experienced more depressive symptoms.[10]

The primary treatment for aggressive behavior involves the use of medications and non-pharmacological treatments such as behavioral approaches or electroconvulsive therapy.[4] Clozapine may still be the most effective drug in reducing aggression. However, its use implies a risk of hematological side effects, so full blood count monitoring is required throughout the treatment. It may increase the already high non-adherence seen in schizophrenia.[3] Furthermore, in many cases, it is necessary to use more than one psychotropic drug, which can increase the burden of side effects, including sedation, akathisia, and dystonia.[15] It is estimated that 8–30% of patients do not respond to these treatments. For this reason, neurosurgical procedures emerge as a therapeutic option.[11]

Although abnormalities in various parts of the brain have been associated with increased aggression, studies in humans and other mammals indicate that the amygdala and the hypothalamus are key components of a broader neural circuit that modulates aggressive behavior,[19] which is why they have become targets of interest for ablative management in patients with refractory aggressive disorders.

In 1970, Mark and Ervin published the book "Violence and the Brain,"[14] with important contributions from Dr. José Delgado. In their work, the authors explain, based on their experience with brain stimulation in patients with temporal lobe epilepsy, how pathological aggression and uncontrolled violence can be the result of damage to deep structures of the temporal lobe, such as the amygdala. They proposed psychosurgery through ablative lesions as a tool for the management of pathological aggressiveness, even proposing it as a treatment for social or penal rehabilitation of young offenders.[6]

The posteromedial hypothalamus is an important sympathetic center, so theoretically, ablative treatments at this level could generate, among other effects, sympathetic hypertonia with an increase in mean arterial pressure, tachycardia, and thermoregulatory disruption.[17] Despite this association, Gouveia *et al*.,[8] have reported in a historical review of 243 published cases where the percentage of permanent complications associated with this procedure was low, with an improvement in aggressive behavior of approximately 80%.

The amygdala is critical in processing threatening stimuli and mediating autonomic, neuroendocrine, and behavioral responses.[13] The central nucleus is a prominent output region for expressing innate emotional responses and their associated physiological processes.[23] The mechanism is responsible for the marked reduction in aggressive behavior observed after the amygdala lesion could be related to an increase in tolerance to provocation and a decline in the level of autonomic arousal.[9] Although some cases of a decrease in social dominance[20] and Klüver-Bucy syndrome[12] have been reported, mainly in bilateral lesions, ablative treatment in the amygdala has been reported as safe, with few adverse effects and no impairment of overall intelligence and global memory.[8,24]

In our case, we decided to perform a two-stage bilateral hypothalamotomy and unilateral amygdalotomy due to the reported increased risk of complications in bilateral lesions.[8] Moreover, we consider that GKR, a non-invasive procedure, has a lower risk of complications than other ablative techniques, such as bipolar radiofrequency catheter ablation. On the other hand, it does not require the implantation of external devices (catheters and pulse generators) as in Deep brain stimulation, which, although it could be an attractive alternative for treating these disorders given the reversible nature of its effect, could also increase the anxiety of patients with mental illness carrying unusual devices implanted in their heads.

CONCLUSION

Hypothalamotomy plus amygdalotomy with Gamma Knife may be as effective as other open ablative techniques for the management of refractory aggressive disorder in patients with mental illness, with a differential capacity to provide a better safety profile given its non-invasive nature.

Ethical approval

The research/study was approved by the Institutional Review Board at Fundación Clínica Shaio, number DIB 43–4, dated November 10, 2023.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

REFERENCES

1. Aas IM. Guidelines for rating global assessment of functioning (GAF). Ann Gen Psychiatry 2011;10:2.
2. American Psychiatric Association. Diagnostic and Statistical manual of mental disorders. Vol. 64. Arlington, VA: American Psychiatric Association; 2013.
3. Cramer JA, Rosenheck R. Compliance with medication regimens for mental and physical disorders. Psychiatr Serv 1998;49:196-201.
4. Citrome L, Volavka J. The psychopharmacology of violence: Making sensible decisions. CNS Spectr 2014;19:411-8.
5. Devaramane V, Pai NB, Vellu SL. The effect of a brief family interventions on primary carer's functioning and their schizophrenic relatives' levels of psychopathology in India. Asian J Psychiatry 2011;4:183-7.
6. Faria MA. Violence, mental illness, and the brain-a brief history of psychosurgery: Part 3-from deep brain stimulation to amygdalotomy for violent behavior, seizures, and pathological aggression in humans. Surg Neurol Int 2013;4:91.
7. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. Lancet 2017;392:1789-858.
8. Gouveia FV, Hamani C, Fonoff ET, Brentani H, Alho EJ, De Morais RM, *et al*. Amygdala and hypothalamus: Historical overview with focus on aggression. Neurosurgery 2019;85: 11-30.
9. Hitchcock E, Cairns V. Amygdalotomy. Postgrad Med J 1973;49:894-904.
10. Huang ZH, Wang F, Chen ZL, Xiao YN, Wang QW, Wang SB, *et al*. Risk factors for violent behaviors in patients with schizophrenia: 2-year follow-up study in primary mental health care in China. Front Psychiatry 2023;13:947987.
11. Jiménez F, Soto JE, Velasco F, Andrade P, Bustamante JJ, Gómez P, *et al*. Bilateral cingulotomy and anterior capsulotomy applied to patients with aggressiveness. Stereotact Funct Neurosurg 2012;90:151-60.
12. Kluver H, Bucy PC. "Psychic blindness" and other symptoms following bilateral temporal lobectomy. Am J Physiol 1937;119:254-84.
13. LeDoux J. The amygdala. Curr Biol 2007;17:R868-74.
14. Mark VH, Ervin FR. Violence and the brain. NewYork: Harper and Row; 1970.
15. Morrissette DA, Stahl SM. Treating the violent patient with psychosis or impulsivity utilizing antipsychotic polypharmacy and high-dose monotherapy. CNS Spectr 2014;19:439-48.
16. Oliver PC, Crawford MJ, Rao B, Reece B, Tyrer P. Modified overt aggression scale (MOAS) for people with intellectual disability and aggressive challenging behaviour. A reliability study. J Appl Res Intellect Disabil 2007;20:368-72.
17. Otero A, Pérez B, Ríos-Quintero AF, Sánchez-Escobar A, Ocampo C. Hypothalamotomy in patients with treatment-resistant aggressiveness: functional outcomes. Rev Neurol 2020;71:93-8.
18. Perlman CM, Hirdes JP. The aggressive behavior scale: A new scale to measure aggression based on the minimum data set. J Am Geriatr Soc 2008;56:2298-303.
19. Rosell DR, Siever LJ. The neurobiology of aggression and violence. CNS Spectr 2015;20:254-79.
20. Rosvold HE, Mirsky AF, Pribram KH. Influence of amygdalectomy on social behavior in monkeys. J Comp Physiol Psychol 1954;47:173-8.
21. Senior M, Fazel S, Tsiachristas A. Tsiachristas the economic impact of violence perpetration in severe mental illness: A retrospective, prevalence based analysis in England and Wales. Lancet Public Health 2020;5:e99-106.
22. Siever LJ. Neurobiology of aggression and violence. Am J Psychiatry 2008;165:429-42.
23. Swanson LW, Petrovich GD. What is the amygdala? Trends Neurosci 1998;21:323-31.
24. Torres CV, Martínez N, Ríos-Lago M, Lara M, Alvarez-Linera J, Cabanyes J, *et al*. Surgery and radiosurgery in autism: A retrospective study in 10 patients. Stereotact Funct Neurosurg 2021;99:474-83.

How to cite this article: Molina-Romero OI, Diez-Palma JC, Fonnegra-Caballero A, Segura-Hernández A, Matinez-Alvarez R, Yamhure E, *et al*. Bilateral hypothalamotomy plus dominant amygdalotomy with Gamma Knife radiosurgery. A non-invasive alternative when everything has failed in the management of aggressive behavior disorder. Surg Neurol Int. 2024;15:469. doi: 10.25259/SNI_860_2024