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CO_2 Laser Ablation for the Manifestations of Multiple Cutaneous Neurofibromas in an Adult with Neurofibromatosis Type 1: A Case Report

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Nicholas Calvin[1,2]

[1] Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Australia

[2] Faculty of Medicine, Universitas Indonesia, Indonesia

Introduction Neurofibromatosis type 1 (NF-1) is a genetic disorder, usually manifested with the slow growth of benign neurocutaneous tumors that form near the spinal cord and peripheral nerves in the body. In most cases, NF-1 is usually diagnosed during infancy or early childhood. However, in some cases, children and adults without family history may have a spontaneous genetic mutation of an unknown cause. There are several modalities to treat NF-1, which include conventional surgery removal and CO_2 laser ablation. The review of literature aims to explore the advantages and disadvantages of CO_2 laser ablation, in comparison to conventional surgery

Case presentation A 32-year-old postpartum Australian woman is presented to the neurosurgery department outpatient clinic. When she was around 20 years old, non-painful multiple benign lumps along her spine and peripheral nerves with multiple *café au lait* spots started to appear. Both size and numbers of these lumps gradually increase as she ages. The patient is diagnosed with NF-1, according to the NIH consensus development conference. The patient is then scheduled to go to NF clinic 2 (two) months after the meeting, in which the patient is planned to undergo a treatment of CO_2 laser ablation.

Conclusions Studies have shown that CO_2 laser ablation has outperformed conventional surgery in managing the clinical manifestation of NF-1. CO_2 laser ablation has better cosmetic outcomes, a lesser number of adverse events, and is less time-consuming

Keywords *neurofibromatosis type I, von Recklinghausen's disease, adult, postpartum woman, CO_2 laser ablation*

Correspondence to:
Nicholas Calvin
Faculty of Medicine,
Universitas Indonesia,
Indonesia

nicholaspaulus.calvin@gmail.com

Introduction

Neurofibromatosis type 1 (NF-1), also known as von Recklinghausen's disease, is a rare condition that is usually manifested with the slow growth of benign neurocutaneous tumors that form near the spinal cord and peripheral nerves in the body.[1-4] Besides NF-1, there are two other types of neurofibromatosis (NF), which are NF-2 and Schwannomatosis. These three NFs represent completely distinctive conditions that affect three different loci (NF-1 is located in chromosomal region 17q11.2, NF-2 in 22q12.2, and Schwannomatosis in 22q11.23).[5-8] Most people with one type of NF are extremely unlikely to develop other types of NF.[5] Of these three conditions, NF-1 contributes to approximately 90% of all NF cases.[2, 3]

In most cases, NF-1 is usually diagnosed during infancy or early childhood. However, in some cases, some patients without family history may have a spontaneous genetic mutation of an unknown cause.[9] The common manifestations of NF-1 include multiple *café au lait* spots (flat discoloration patches on the skin), cutaneous and/or subcutaneous neurofibromas, Lisch nodules, and freckles or lumps in the axillary and groin.[9] In a clinical study by McGauhran et al., 18% of adults with NF-1 may develop plexiform neurofibromas (affecting multiple other nerves, including the eye socket, neck, and pelvis).[10] Unlike NF-1, plexiform neurofibromas can have a cancerous growth, called peripheral nerve sheath tumors (MPNSTs). Patients with plexiform neurofibromas should immediately inform their doctors if they develop new persistent pain and other symptoms such as numbness and weakness in the limbs.[10]

Even though most neurofibromas are benign, these tumors may be painful and often lead to psychological or social distress.[11] There are two main reasons for the excision of these neurofibromas: for medical and/or cosmetic reasons.[11] Up until now, there is no conservative treatment that is able to stop the growth of NF-1, thus the only way to remove cutaneous neurofibromas is through surgical interventions.[12] Some studies suggested that using a scalpel for the removal of NF-1 has several disadvantages, especially for adult patients.[13] Some disadvantages include time-consuming procedure; high incidences of intra- and postoperative bleeding; and only a small part of NF can be removed at one time. Another way to remove multiple NF is by using CO_2 laser ablation.[13] Some studies suggest that removing NF-1 by using this type of method is more effective and efficient.[13-17] Therefore, in this case report, the author would like to report an adult patient that is planned to undergo laser intervention for the treatment of NF-1 after an outpatient meeting. This case report will also be supported by the review of several studies, which includes randomized controlled trials (RCTs) and cohort studies. The aim of the literature review is to explore the advantages and disadvantages of CO_2 laser ablation, in comparison to conventional surgery, for the treatment of NF-1 patients

Case Presentation

A 32-year-old postpartum Australian woman is presented to the neurosurgery department outpatient clinic. She is accompanied by her husband, and she has a one-month-old male baby. She neither had a significant medical history nor was she taking any medications prior to this. When she was around 20 years old, non-painful multiple benign growths along her spine and peripheral nerves and multiple café au lait spots started to appear. The size and numbers of growth and spots gradually increased as she aged. She did not have any family history of having NF-1. She had not done any NF-1 testing. The patient had not consulted any doctors regarding her condition until an obstetrician told her to consult a neurologist or neurosurgeon during one of her third trimester antenatal care. Her baby was found to have multiple hyperpigmented skin macules.

Physical Examination

General examination: normal blood pressure (120/80 mm Hg), normal temperature (37 °C), normal cardiac auscultation.

Dermatological status: multiple cutaneous neurofibromas, which vary in size (few millimeters to several centimeters), with one large, painful bump near her upper lumbar area if pressed (diameter >4 cm), axillary freckling, and several *café au lait* spots (diameter >1.5 cm).

Ophthalmological status: Lisch nodules on both iris without clinical involvement.

Diagnosis

The diagnosis of this patient is NF-1 with differential diagnosis of other forms of neurofibromatosis or other conditions that have skin manifestations similar to *café au lait*. However, in accordance with the National Institute of Health (NIH) consensus development conference guideline (Table 1), the clinical diagnosis of NF-1 can be made according to the presence of two or more of the seven diagnostic criteria. This patient has fulfilled four criteria as follows:[18]

1) Six or more *café au lait* macules over 15 mm in the greatest diameter
2) Two or more cutaneous or subcutaneous neurofibromas
3) Freckling in the axillary
4) Two or more Lisch nodules (iris hamartomas)

Table 1. NF-1 clinical diagnostic criteria based on NIH consensus development program[18].

Clinical diagnostic criteria for NF-1:
1) Six or more café au lait macules over 5 mm in the greatest diameter in prepubertal individuals and over 15 mm in the greatest diameter in post-pubertal individuals.
2) Two or more neurofibromas of any type *or* one plexiform neurofibroma.
3) Freckling in the axillary or inguinal region.
4) Optic glioma.
5) Two or more Lisch nodules (iris hamartomas)
6) A distinctive osseous lesion such as sphenoid dysplasia or thinning g of

	long bone cortex with or without pseudoarthrosis
7)	A first-degree relative (parent, sibling or offspring) with NF-1 by the above criteria.

Follow-Up Plan

The patient is scheduled to go to NF clinic 2 (two) months after the meeting in which the patient is planned to undergo the treatment of CO_2 laser ablation. Other than that, the patient is also required to do radiology examinations and a lab test to rule out the possibility of plexiform neurofibromas: (1) Magnetic Resonance Imaging, (2) CT Scan, and (3) urinalysis.

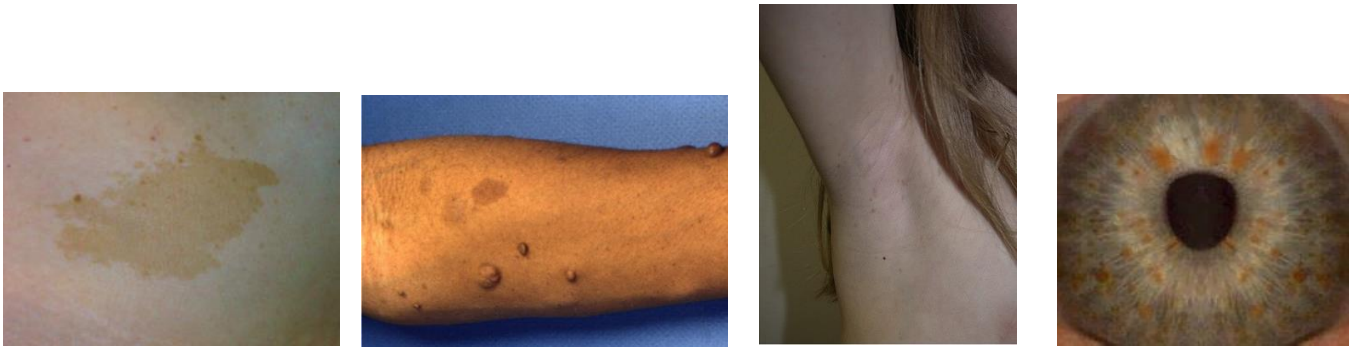

Fig 1. Clinical manifestations of NF-1 that were found on the patient. (A) café-au-lait macules over 15 mm19, (B) subcutaneous neurofibromas[20], (C) axillary freckling[21], (D) Lisch nodules (iris hamartomas)[22]

Methodology

Data Sources and Search Strategy

A literature search was done on Medline (Ovid) on 23rd February 2020. The keywords used were "neurofibromatosis type I" or "von Recklinghausen's disease" in conjunction with "CO_2 laser ablation" and "adults" or "adolescents". The search was limited to studies written in English. Articles without the availability of full-text articles will not be looked at further. Five articles that fulfill all the inclusion and exclusion criteria were then analyzed and taken into deeper analysis. The full search strategy was presented in Appendix 1.

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria were made based on population, intervention, comparator, and outcomes (PICO) components. However, to fully compare between CO_2 laser ablation and conventional surgery procedure, no outcome indicator was specified. The following Table 2 shows the full inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Human studies (adults or adolescents)	Pediatric subjects
Subjects were diagnosed with NF-1, according to the NIH consensus	Animal studies

development conference guideline	
Treatment-arm subjects underwent CO_2 laser ablation procedure	Single arm studies
Control-arm subjects underwent conventional surgery procedures	Non-English language studies
English language studies	
Full-text article available	

Data Extraction and Analysis

Data extraction was done by one author (NC) by choosing several articles that fulfill all the eligibility criteria. Screened studies were then assessed using the critical appraisal tools, respective to their type of studies. Five chosen high-quality studies were then included for further analysis.

Quality Assessments

The quality of the five included studies was assessed using standardized critical appraisal tools. The quality assessments were completed by one single author (NC). RCTs were evaluated using the PEDro scale, while cohort studies were assessed using the JBI critical appraisal checklists.[23,24] The full results of the assessments are provided in Appendix 2.

Results

Search Findings

The search was conducted on Medline (Ovid) on 23rd February 2020. A total of 5 studies, which consist of 2 RCTs and 3 cohort studies, were included for analysis of this study. Data extraction and quality assessment were done after this process. Data analysis was done narratively without synthesizing the results of studies. The evidence from included studies was used to answer and support the research question.

Quality Assessments of included studies

Two RCTs were assessed using the PEDro scale and three cohort studies were assessed using the JBI critical appraisal tool. [23,24] All studies are high-quality studies.[25-29]

Discussion

Clinical manifestations of NF-1 are often distressing for the patient. Although benign, most patients seek treatment for either medical and/or cosmetic reasons. The discussion below is based on five high-quality studies that were assessed using their respective quality appraisal tools.

Based on an RCT of 500 NF-1 patients, Bata et al. reported that *café au lait* macules are present in the NF-1 population mean of 98%, neurofibromas in 52%, and skeletal anomalies in 14%.[25] As much as 56% of NF-1 cases, the patient had *de novo* mutation without a family history of NF-1. Approximately 2% of all NF-1 patients may develop cancerous growth of malignant nerve sheath tumor.[25]

Conventional surgery has been used to manage NF-1 patients. However, this type of management modality is considered to

be exceedingly time-consuming, disfiguring, and costly.[13] Therefore, in the past decade, the use of laser ablation (electrosurgery) for the management of NF-1 has been gradually increasing.[26] Algermissen et al. report that out of 119 NF-1 patients treated with CO_2 laser ablation, most of the patients reported a significant increase in confidence and social acceptance. Only 2.5% (3/119) of patients developed hypertrophic scars, which should be less than conventional surgery.[26] Another study by Miyawaki et al. reported the incidence of hematoma and white wide scar in NF-1 patients treated with conventional surgery was 16.4% (11/67).[27] However, the study by Algermissen et al. was a single-arm study, thus more research and studies need to be done to further prove the available evidence.[26] Moreover, CO_2 laser therapy is proven to be less time-consuming in comparison with conventional surgery, since it may treat multiple neurofibromas at one time and also has a low risk of scarring that may alter cosmetic outcomes in comparison to conventional surgeries.[27]

Other than just surgery or electrosurgery to remove the manifestations of the NF-1, high-intensity monitoring should also be done on the postpartum woman, as one of the case reports reported that a patient that had vascular involvement of NF-1 may develop spontaneous hemothorax 16-24 hours after labor.[28] It is hypothesized that the spontaneous hemothorax was developed due to the exacerbated NF-1 vascular pathology and hemodynamic changes during labor.[28] This complication should be prevented by increasing the monitoring frequency for the patient since it can be fatal if not treated and monitored well.[28]

As the alternative to CO_2 laser ablation therapy, there is another type of electrosurgery, which is called the erbium: yttrium-aluminum-garnet (Er:YAG) thermal ablation. Er:YAG laser ablation has a minor thermal change compared to CO_2 laser ablation, thus causing minimal collagen tightening or effects of hemostasis.[29] Kriechbaumer et al. concluded that Er:YAG laser ablation outperformed both conventional surgery and CO_2 laser therapy with the more rapid procedure, faster recovery, and significantly better cosmetic results.[29]

Limitations and Recommendations

There are several limitations to this study. The patient in this case report was not followed until diagnostic exams, treatments, and after treatments. This case report aims to present a particular case of NF-1 in an adult and to gather literature about the comparison of CO_2 laser ablation and conventional surgery to treat multiple cutaneous neurofibromas. Moreover, the included RCTs were lacking in the blinding process, probably due to the nature of treatment between CO_2 laser ablation and conventional surgery, where it is impossible to blind both subjects and therapists. However, both studies also failed to blind the assessors.[25,29] Furthermore, the methodology of this study could also be redesigned and improved into a systematic review, to further validate the results and conclusions of this study. Future research

on NF-1 may also explore the clinical efficacy and safety of Er:Yag laser ablation in comparison to CO_2 laser ablation and other NF-1 treatment modalities.

Conclusions

In conclusion, studies have shown that CO_2 has outperformed conventional surgery in managing the clinical manifestations of NF-1.[13, 26] CO_2 laser ablation is superior; it leads to better cosmetic outcomes, a lower number of adverse events, and is less time-consuming.[25-27] Patients that underwent CO_2 laser ablation are also reported to have a significant increase in confidence and social acceptance.[26] However, adequate monitoring, especially for postpartum women, should be done since it can lead to fatal complications.[24,28]

Conflict of Interests

None declared.

Funding Sources

None.

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SUPPLEMENTARY MATERIALS

CO_2 Laser Ablation for the Manifestations of Multiple Cutaneous Neurofibromas in an Adult with Neurofibromatosis Type 1: A Case Report

Nicholas Calvin[1, 2]
[1] Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Australia.
[2] Faculty of Medicine, Universitas Indonesia, Indonesia
nicholaspaulus.calvin@gmail.com

Appendix 1: Search Strategy

Database	Date searched	#	Search terms
Medline (Ovid)	23 February 2020	1	exp "neurofibromatosis type 1".mp./
		2	exp "(NF-1 or NF 1)".mp./
		3	exp "von Recklinghausens disease*" OR "von Recklinghausen disease*".mp./
		4	1 OR 2 OR 3
		5	exp "adult*"/ OR exp "adolescent*" NOT (exp "infan*"/ OR exp "child*"/).mp./
		6	exp "co2 laser ablation*" OR "co2 laser therap*" OR "co2 laser surger*" OR "carbon dioxide laser ablation*" OR "carbon dioxide laser therap*" OR "carbon dioxide laser surger*".mp./
		7	4 AND 5 AND 6
		8	Limits: english, full-text available, humans

Appendix 2: Critical Appraisal of Included Studies

Journal 1: Bata et al. (2019)[23,25]

PEDro scale

1.	eligibility criteria were specified	no ❑ yes ❑ where:
2.	subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	no ❑ yes ❑ where:
3.	allocation was concealed	no ❑ yes ❑ where:
4.	the groups were similar at baseline regarding the most important prognostic indicators	no ❑ yes ❑ where:
5.	there was blinding of all subjects	no ❑ yes ❑ where:
6.	there was blinding of all therapists who administered the therapy	no ❑ yes ❑ where:
7.	there was blinding of all assessors who measured at least one key outcome	no ❑ yes ❑ where:
8.	measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	no ❑ yes ❑ where:
9.	all subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"	no ❑ yes ❑ where:
10.	the results of between-group statistical comparisons are reported for at least one key outcome	no ❑ yes ❑ where:
11.	the study provides both point measures and measures of variability for at least one key outcome	no ❑ yes ❑ where:

Appendix 2: Critical Appraisal of Included Studies

Journal 2: Kriechbaumer et al. (2013)[23,29]

PEDro scale

1.	eligibility criteria were specified	no ❑	yes ❑	where:
2.	subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	no ❑	yes ❑	where:
3.	allocation was concealed	no ❑	yes ❑	where:
4.	the groups were similar at baseline regarding the most important prognostic indicators	no ❑	yes ❑	where:
5.	there was blinding of all subjects	no ❑	yes ❑	where:
6.	there was blinding of all therapists who administered the therapy	no ❑	yes ❑	where:
7.	there was blinding of all assessors who measured at least one key outcome	no ❑	yes ❑	where:
8.	measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	no ❑	yes ❑	where:
9.	all subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"	no ❑	yes ❑	where:
10.	the results of between-group statistical comparisons are reported for at least one key outcome	no ❑	yes ❑	where:
11.	the study provides both point measures and measures of variability for at least one key outcome	no ❑	yes ❑	where:

Appendix 2: Critical Appraisal of Included Studies

Journal 3: Miyawaki et al. (2007)[24,27]

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JBI Critical Appraisal Checklist for Cohort Studies

Reviewer Nicholas Calvin Date 24/02

Author Miyawaki et al. Year 2020 Record Number 1

	Yes	No	Unclear	Not applicable
1. Were the two groups similar and recruited from the same population?	☐	☒	☐	☐
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	☒	☐	☐	☐
3. Was the exposure measured in a valid and reliable way?	☒	☐	☐	☐
4. Were confounding factors identified?	☐	☒	☐	☐
5. Were strategies to deal with confounding factors stated?	☐	☒	☐	☐
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	☒	☐	☐	☐
7. Were the outcomes measured in a valid and reliable way?	☒	☐	☐	☐
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	☒	☐	☐	☐
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	☒	☐	☐	☐
10. Were strategies to address incomplete follow up utilized?	☒	☐	☐	☐
11. Was appropriate statistical analysis used?	☐	☒	☐	☐

Overall appraisal: Include ☒ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

Appendix 2: Critical Appraisal of Included Studies

Journal 4: Dubin et al. (2019)[24,28]

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JBI Critical Appraisal Checklist for Case Reports

Reviewer Nicholas Calvin Date 24/02

Author Dubin et al. Year 2020 Record Number 2

	Yes	No	Unclear	Not applicable
1. Were patient's demographic characteristics clearly described?	☐	☒	☐	☐
2. Was the patient's history clearly described and presented as a timeline?	☒	☐	☐	☐
3. Was the current clinical condition of the patient on presentation clearly described?	☒	☐	☐	☐
4. Were diagnostic tests or assessment methods and the results clearly described?	☒	☐	☐	☐
5. Was the intervention(s) or treatment procedure(s) clearly described?	☒	☐	☐	☐
6. Was the post-intervention clinical condition clearly described?	☒	☐	☐	☐
7. Were adverse events (harms) or unanticipated events identified and described?	☒	☐	☐	☐
8. Does the case report provide takeaway lessons?	☒	☐	☐	☐

Overall appraisal: Include ☒ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

Appendix 2: Critical Appraisal of Included Studies

Journal 5: Algermissen et al. (2001)[24,26]

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JBI Critical Appraisal Checklist for Cohort Studies

Reviewer Nicholas Calvin Date 24/02

Author Algermissen et al. Year 2020 Record Number 3

	Yes	No	Unclear	Not applicable
1. Were the two groups similar and recruited from the same population?	☐	☒	☐	☐
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	☒	☐	☐	☐
3. Was the exposure measured in a valid and reliable way?	☒	☐	☐	☐
4. Were confounding factors identified?	☐	☒	☐	☐
5. Were strategies to deal with confounding factors stated?	☐	☒	☐	☐
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	☒	☐	☐	☐
7. Were the outcomes measured in a valid and reliable way?	☒	☐	☐	☐
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	☒	☐	☐	☐
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	☒	☐	☐	☐
10. Were strategies to address incomplete follow up utilized?	☐	☒	☐	☐
11. Was appropriate statistical analysis used?	☐	☒	☐	☐

Overall appraisal: Include ☒ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)