Perceptions Regarding Daith Piercing in Migraine, A Survey of Pediatric Patients

Trevor Gerson *, Mark Connelly, Madeline Boorigie, Jennifer Bickel and Jennifer Dilts

Department of Neurology, Headache Section, Children’s Mercy Kansas City, Kansas City, MO 64108, USA; mconnelly1@cmh.edu (M.C.); meboorigie@cmh.edu (M.B.); jlbickel@cmh.edu (J.B.); jjdilts@cmh.edu (J.D.)

* Correspondence: tgerson@cmh.edu

Received: 28 July 2020; Accepted: 29 August 2020; Published: 31 August 2020

Abstract: The treatment of migraine is evolving to include non-traditional approaches, as pharmacologic therapy alone is unsuccessful in many patients. Daith piercing, a cartilaginous ear piercing, has become popular as a potential nonpharmacological treatment option for migraine. However, there are no systematic data on the utilization and efficacy of these piercings. Therefore, we investigated the perceptions of pediatric patients regarding Daith piercing and gathered initial retrospective data for patients who had already received it. Patients presenting to a pediatric neurology clinic were invited to complete a questionnaire to assess knowledge about and attitudes towards Daith piercing and their willingness to undergo such a treatment. For those with a Daith piercing, the effects on headaches, function, and mood were evaluated. Of the 171 respondents, 61% had prior knowledge of Daith piercings, 27% knew someone with a Daith piercing, and 60% of patients presenting with headache were willing to undergo piercing. Of the eight patients (5% of respondents) who had already undergone piercing, six (75%) reported improvement in headaches, five (62%) had missed fewer days of school or work, and seven (87%) reported mood improvement. The high proportion of pediatric patients willing to undergo this form of treatment speaks to the desire for and acceptance of nonpharmacologic treatments. Although based on a small sample, the data from children who have already undergone Daith piercing is promising and supports a need for further systematic investigation into this treatment approach.

Keywords: Daith; migraine; piercing; pediatric

1. Introduction

Headaches are some of the most common diseases in the world, with the most common types of headache (tension-type headache and migraine) comprising two of the top causes of years lived with disability in the world [1]. In children and adolescents, migraine affects approximately 5% of boys and 7.7% of girls and leads to moderate to severe disability in 28% of those affected [2]. Chronic migraine in particular, defined as having greater than 15 headache days per month (at least eight of which are migraines), occur in 2% of adolescents, and can significantly affect a child’s physical, social, and emotional development [2]. The level of disability in children with migraines has been found to be similar to children with rheumatological diseases or cancer [3].

Preventative pharmacological therapies are used to decrease the frequency and intensity of headaches [4]. However, despite the widespread prevalence of pediatric migraine, there is only one preventive medication (topiramate) which has been approved by the US Food and Drug Administration for use in pediatric patients (ages 12 and over). Off-label use of other medications to treat headaches in children is common [3]. Overall, however, a large percentage of headache patients do not get complete relief with pharmacologic therapies [6]. Further, certain medications such as opioids or butalbital
that are sometimes used (against recommendations) to treat pediatric migraine can lead to worsening headaches and disability in the future [7–9].

The high prevalence of headaches in children and low efficacy of medical therapies for at least a subset of patients may lead some families to seek nonpharmacologic treatments. Data from two national health surveys have shown that 30% of respondents aged 10–17 years with headache reported using complementary and alternative medicine (CAM) modalities, compared to 17% in those without headache [4]. Similar interest in CAM modalities has been reported in other studies of youth with chronic pain. In one study using data from the National Health Interview Survey, over 1 in 5 youth with a chronic pain condition (headache, abdominal pain, or musculoskeletal pain) had used CAM in the prior year, compared to use in less than 1 in 10 youth without a chronic pain condition [10]. In clinical samples of youth with headache or another chronic pain condition, the proportions of patients that had already tried a CAM modality are even higher (40–60%) [11,12]. The most commonly used CAM modalities among children with chronic pain were found to be biology-based therapies (special diets and herbal supplements) and body-based therapies (e.g., chiropractice). Common reasons reported by parents of youth with chronic pain for seeking out CAM include that these treatments are “natural” and that they can improve general wellness. Over half of parents of youth with chronic pain report that CAM use led to improved overall health for their child [10].

In the past few years, a specific ear cartilage piercing, the Daith piercing (Figure 1), has become popular as an unconventional treatment that may have benefit for migraine. The Daith piercing has received widespread media coverage [13,14]. Similar to the findings of relatively high interest in CAM modalities among youth with headaches or other chronic pain conditions, we have found in our pediatric headache clinic that patients with migraine frequently ask about the Daith piercing. However, a literature search at the time returned no data to use when counseling patients and their parents.

![Figure 1. Daith piercing (with permission of the patient and her mother), showing the piercing through the crus helix.](image)

We undertook the current study to better understand attitudes toward and experiences with Daith piercing as a headache treatment modality in our pediatric population. Specifically, we aimed to formally investigate our anecdotal findings that this was a subject in which patients were interested and were willing to undergo such a treatment. We also hoped to gather data from any patients who had already undergone Daith piercing in order to gain preliminary understanding of the risks and benefits of the treatment, and to determine whether a future prospective study might be warranted based on results. Since the completion of the current study, two case reports have now been published [15,16] but still no systematic investigations have been completed.
2. Materials and Methods

The Children’s Mercy Kansas City (CM) Institutional Review Board approved this study (# 16110851). A convenience sample of patients who presented to the CM pediatric neurology clinic between July 2017 and December 2017 were eligible to participate, in an effort to maximize sample size within the approved study time period, and as there are patients who are seen in the general neurology clinic for headache rather than only in the headache clinic. This also allowed the comparison of primary headache patients to general neurology patients as controls. Participants completed a one-time questionnaire (Supplementary File) administered by clinic or research staff during their clinic visit. The questionnaire was developed by the study team to assess patients’ knowledge about Daith piercing and willingness to undergo the piercing. For patients who had undergone Daith piercing, they were prompted to answer additional questions about its perceived effect on headaches, function, and mood, as well as to report on any adverse events they experienced from the procedure. A demographic questionnaire also was administered to obtain data on participant characteristics including sex, age, race, ethnicity, primary language spoken at home, parents’ highest level of education, and household income.

Survey data were analyzed with the Statistical Package for the Social Sciences (SPSS) software (IBM). Descriptive statistics, chi-square tests, and point biserial correlations were used to describe the sample and to determine the association of demographic variables with Daith piercing attitudes and experience. Subgroup analyses of patients presenting with the chief complaint of headache were performed and then compared to non headache patients as a general control. Missing data were managed using case-wise deletion.

3. Results

3.1. Descriptive Statistics

The survey was completed by 171 patients, 119 (70%) of which described the primary reason for their visit as headache. Demographic information is provided in Table 1 and is generally representative of our patient population. Descriptive statistics for the responses to survey questions are provided in Table 2. Age appeared to be incorrectly reported on some surveys; ages ranged from 3 to 53, suggesting that in some cases the parent or guardian filling out the survey responded with their own age rather than that of the child. To account for this, for all analyses involving age, a cutoff of age 22 (the upper limit for patients seen in the clinic) was used. Additionally, analyses to look at ethnicity effects on survey responses could not be validly done, as only 6 survey respondents identified as Hispanic or Latino.
Table 1. Demographic information for all respondents and for those who indicated headache as the primary reason for their clinic visit.

| Variables                              | Primary Headache Patients (n = 119) | Non-Headache Patients (n = 51) | Total Patients (n = 170) | Missing |
|----------------------------------------|------------------------------------|--------------------------------|--------------------------|---------|
| Age (Median, Standard Deviation)       | 14 (3.14)                          | 12 (6.67)                      | 14 (4.18)                | 43 (25%)|
| Female/Male                            | 74 (62%)/34 (29%)                  | 33 (65%)/13 (26%)              | 108 (63%)/47 (27.5%)     | 16 (9.4%)|
| Caucasian race                         | 90 (75.6)                          | 39 (77%)                       | 130 (76%)                | 18 (10.5%)|
| Hispanic or Latino ethnicity           | 3 (2.5%)                           | 3 (5.9%)                       | 6 (3.5%)                 | 28 (16.4%)|
| Internet access at home                | 102 (86%)                          | 41 (80%)                       | 144 (84%)                | 17 (9.9%)|
| Cell phone owners                      | 101 (85%)                          | 40 (78%)                       | 142 (83%)                | 17 (10%)|
| Highest level of education (Father)    |                                    |                                |                          |         |
| Some high school                       | 10 (8.4%)                          | 6 (12%)                        | 16 (9.4%)                | 24 (14%)|
| High school                            | 21 (17.6%)                         | 7 (14%)                        | 28 (16.4%)               | -       |
| Some college/technical school          | 39 (32.8%)                         | 13 (26%)                       | 53 (31%)                 | -       |
| College degree                         | 23 (19.8%)                         | 11 (22%)                       | 34 (19.9%)               | -       |
| Post college degree                    | 9 (7.6%)                           | 7 (14%)                        | 16 (9.4%)                | -       |
| Highest level of education (Mother)    |                                    |                                |                          |         |
| Some high school                       | 3 (2.5%)                           | 3 (6%)                         | 6 (3.5%)                 | 18 (10.5%)|
| High school                            | 19 (16%)                           | 4 (8%)                         | 23 (13.5%)               | -       |
| Some college/technical school          | 28 (23.5%)                         | 18 (35%)                       | 46 (26.9%)               | -       |
| College degree                         | 45 (37.8%)                         | 14 (28%)                       | 59 (34.5%)               | -       |
| Post college degree                    | 12 (10.1%)                         | 7 (14%)                        | 19 (11.1%)               | -       |
| Median household income (category)     | $70,000–$79,999                     | $50,000–59,999                  | 8 (16%)                 |         |
Table 2. Relationship of participant demographic variables with knowledge and experience of Daith piercing. p-values are reported in parentheses.

| Variables                        | Prior Knowledge of Daith | Personal Contact with Someone with Daith | Has Had A Daith | Willing to Try Daith |
|---------------------------------|--------------------------|------------------------------------------|-----------------|---------------------|
| Chi Square Analyses             |                          |                                          |                 |                     |
| Female sex                      | 5.96 (0.015)             | 3.52 (0.061)                             | 2.52 (0.284)    | 7.0 (0.008)         |
| Caucasian race                  | 2.23 (0.693)             | 7.08 (0.069)                             | 0.47 (0.925)    | 7.32 (0.676)        |
| Owning a cell phone             | 2.054 (0.152)            | 0.019 (0.890)                            | 0.508 (0.776)   | 17.46 (0.002)       |
| Internet access                 | 0.005 (0.944)            | 0.847 (0.357)                            | 0.586 (0.746)   | 4.402 (0.354)       |
| Correlations (Point-Biserial)    |                          |                                          |                 |                     |
| Age                             | 0.124 (0.165)            | 0.125 (0.247)                            | 0.114 (0.286)   | 0.245 (0.007)       |
| Highest level of education of the father | 0.017 (0.840)        | -0.03 (0.972)                            | -0.068 (0.491)  | -0.065 (0.45)       |
| Highest level of education of the mother | -0.028 (0.734)    | -0.134 (0.168)                           | -0.066 (0.495)  | -0.14 (0.093)       |
| Family’s annual household income | -0.081 (0.332)         | -0.176 (0.074)                           | -0.072 (0.465)  | -0.199 (0.019)      |

3.2. Knowledge of and Willingness to Try Daith Piercing

Of all respondents, 104 (61%) reported having prior knowledge of Daith, and 47 (27%) knew someone with a Daith piercing. A total of 92 (54%) respondents were willing to undergo piercing (responded with “somewhat agree” or “strongly agree”). Of the 119 respondents with headache as the primary reason for the visit, 71 (60%) reported being willing to undergo Daith piercing (Figure 2).

Figure 2. Participant level of agreement about their willingness to try Daith piercing.

Sex was significantly associated with increased prior knowledge of Daith piercing, $\chi^2 (1) = 5.96, p = 0.015$. Specifically, females were more likely to have reported that they had prior knowledge of Daith piercing than males. There also was a similar association of sex and willingness to try Daith, with females being disproportionately more willing, $\chi^2 (1)= 3.52, p = 0.06$. Age was found to be positively correlated with being willing to try Daith piercing $r_{pb} = 0.245, p = 0.007$. Owning a cell...
phone was also associated with willingness to try Daith $\chi^2 (1) = 17.5, p = 0.002$. There was a negative correlation between household income and willingness to undergo Daith piercing, $r_{pb} = -0.199, p = 0.019$. There were no statistically significant associations between access to the internet and knowledge of or willingness to try Daith piercing.

3.3. Experiences of Participants Having Undergone Daith Piercings

Out of all respondents, 8 respondents (5%) reported having undergone Daith piercing. Of these patients, 6 (75%) indicated that their headaches were less severe and less frequent, 5 (62%) stated that they missed fewer days of school or work, and 7 (87%) stated that their mood was improved. Only 1 patient (12%) reported an infection at the piercing site. No other adverse events were reported.

4. Discussion

To our knowledge, this is the first study to evaluate the attitudes and experience of pediatric patients regarding Daith piercing. We found that among treatment-seeking youth attending a pediatric neurology clinic, most had prior knowledge of Daith piercing. The majority of the overall sample, and of those specifically being evaluated for headaches, reported an openness to undergo Daith piercing as a treatment option. Thus, we observed a high degree of acceptability for Daith piercing among pediatric patients. Openness and knowledge pertaining to Daith piercing was systematically greater among females and Caucasian patients and, to a lesser extent, those with lower income. We also found that among the small minority of participants who had already undergone Daith piercing, most reported positive outcomes, including improved headaches, functioning, and mood. All but one patient who had tried Daith piercing reported having no adverse events.

In the current study we found that the majority of survey respondents had heard of Daith piercing and would be receptive to undergoing Daith piercing. This suggests that a future prospective trial to systematically evaluate efficacy would likely be successful in recruiting patients. This also empirically demonstrates the need for healthcare providers to have information with which to counsel patients regarding Daith piercing as a treatment option.

Of the small percentage of patients who had undergone Daith piercing, the majority reported improvement in headaches, functioning, and mood, with only one report of a minor adverse effect. Though it is difficult to draw firm conclusions from a small set of data, the reported favorable benefit-to-risk ratio suggests that more study may be indicated and that this treatment should not be dismissed outright when brought up by patients.

The results of our study regarding attitudes toward Daith piercing are comparable with the larger literature on attitudes toward and use of CAM therapies to supplement pharmacological treatments of pain [17]. According to the 2012 National Health Interview Survey, 30% of youth (ages 10–17) with headaches used CAM in the prior 12 months, and 38% of adults with headache have used CAM in the same timeframe [17,18]. In an age where patients and their parents are seeking long-term non-medication options for headache control, treatments such as Daith piercing, if found by more systematic research to be safe and effective, may offer yet another alternative to traditional medications.

Unlike some other CAM therapies, Daith piercing does not require repeat visits to a CAM practitioner, thus potentially saving time and money. In addition, it is unlikely that Daith piercing would have any interactions with other traditional headache treatments.

In adult populations, there have been numerous internet-based questionnaires of Daith piercing that have shown promising results. However, adult data cannot necessarily be extrapolated to pediatrics. Further, results of internet-based surveys should be viewed critically, as they have not undergone peer review and provide a poor level of evidence by virtue of respondent bias. With these caveats in mind, internet surveys of adult patients have similarly shown promising findings for Daith piercing. A summary of three invited surveys of adults performed by the London Migraine Clinic (2 English and 1 Danish), with aggregated results of 1262 patients, was posted online in 2017. This group found that 37% of patients ceased having migraines, and another 30% had one migraine
The number of patients with a constant headache decreased from 6% prior to piercing to 1% after piercing. Patients who had noncontinuous headaches daily decreased from 7% to 2% as well. Interestingly, an average of 70% of patients across the three studies indicated that their use of triptans (a prescription abortive medication for headaches) decreased or stopped completely after Daith piercing. In the London Migraine Clinic study, there were relatively few adverse effects reported, although a number of patients reported that effects persisted for greater than 12 months. The most common adverse events reported were redness, weeping, crusting, and irritation. Approximately 1 in 10 respondents in the English studies reported no symptom improvement, and 17.3% reported no improvement in the Danish study [19].

Another survey about Daith piercing was conducted by the website migrainepal.com. In this study of 1107 participances, questions were asked regarding length of time since Daith piercing and the perceived effect of Daith piercing on migraine frequency and severity. In 18% of patients, migraines were reported to have ceased completely. In another 64% of patients, there was at least a 10% decrease in frequency of migraines. Notably, 5% of respondents reported an increase in the frequency of their migraines. In terms of migraine severity, 66% indicated that this was improved with Daith piercing, with 14% responding to this question that they no longer had migraines. Again, 5% responded that the severity of their migraines increased. Of the 39 patients who had their piercing for more than two years, 12 indicated that they had sustained remission of migraines [20].

The mechanisms of how Daith piercing may provide benefit for headaches are unclear. One hypothesis is that the piercing may activate auricular acupuncture points. There are 43 auricular acupoints that have been proven therapeutic, according to the World Health Organization [21,22]. Multiple studies have shown that auricular acupuncture is an effective migraine treatment [23–25], including at least one small pediatric study [26]. It may be that positive effects of both Daith piercing and auricular acupuncture are mediated by the release of endogenous opioids, neurotransmitters, and/or activation of gate-control mechanisms of pain modulation. Auricular acupuncture, in particular, is thought to provide pain relief through modulation of the reticular formation, as well as the effects on the sympathetic and parasympathetic nervous systems [27]. Functional MRI studies have shown activation of multiple regions of the brain involved in pain signaling, including the somatosensory cortex, amygdala, anterior cingulate, and cerebellum [28]. Another study showed that true acupuncture (but not sham acupuncture) showed increased connectivity in the anterior cingulate, periaqueductal gray, amygdala, and hippocampal formation [29]. Additionally, auricular acupuncture activates the vagal nerve. Neuromodulation devices that activate the vagal nerve have been show to preventively and acutely treat headaches. It is possible that the Daith piercing also activates the vagal nerve [30,31].

Yet another potential mechanism for perceived benefit from Daith piercing is a placebo response. A high rate of placebo responding has been observed in headache treatment studies. A placebo response is not equivalent with no effect; rather, it suggests that the behaviors associated with doing a treatment (such as taking a pill or getting an ear piercing) are contributing to positive outcomes by activating the body’s own endogenous pain response system. For example, it has been shown that placebo increases concentrations of endogenous opioids in cerebrospinal fluid (CSF) in patients with chronic pain [32]. With such a tangible treatment as Daith piercing, a placebo response could be as or more robust than that of oral medications. The effect may even be more pronounced if there is counseling by physicians that this may be a helpful treatment, as it has been found that expectation enhances the response [33].

Our study has several limitations that need to be considered when interpreting results. Of the respondents, 18 (11%) did not provide their age on the study questionnaire. Additionally, 29 respondents (17%) reported an age above 21 years. Since we surveyed patients at a pediatric clinic, it is possible that patients’ parents completed the survey based on their own perceptions, instead of those of their children. Parents were instructed to assist in responding to the survey for children under the age of 13. Some questions were left blank, resulting in missing data for some respondents. Additionally, for the patients who had undergone Daith piercing, recall bias could affect their answers regarding
the effect of Daith piercing on headaches, mood, and functioning. Survey respondents were patients being seen in a pediatric neurology clinic, including patients at a tertiary headache clinic. This group may have more refractory symptoms than patients presenting to primary care providers. Therefore, these patients may be more aware of and receptive to alternative treatments such as Daith piercing, when compared to headache patients presenting to their primary care providers.

Future prospective studies regarding Daith piercing in patients with migraine, though seemingly warranted, would have several obstacles. The first is how to blind such a procedure, as the placebo benefit of this treatment is not yet known (and there are no other clearly comparable interventions). Furthermore, a specific protocol for Daith piercing would need to be developed to standardize the procedure (i.e., single piercing versus bilateral; ipsilateral side to pain versus contralateral).

5. Conclusions

The majority of patients being seen in pediatric neurology clinics, and particularly patients being evaluated for headaches, appear to have heard of Daith piercing and are seemingly willing to undergo Daith piercing. The willingness to consider Daith piercing speaks to the desire for and acceptance of nonpharmacologic treatment in pediatric patients with headache. The data from those who have already undergone Daith piercing, though small, warrants further systematic investigation into the safety and efficacy of this intervention.

Supplementary Materials: The following are available online at http://www.mdpi.com/2571-8800/3/3/22/s1.

Author Contributions: T.G.: Conceptualization, methodology, formal analysis, writing (original draft, review and editing), visualization; M.C.: Conceptualization, methodology, validation, investigation, writing—review and editing, supervision; M.B.: Investigation, resources, project administration, data curation; J.B.: Conceptualization, methodology, writing—review and editing, supervision, project administration; J.D.: Methodology, investigation, resources, writing—review and editing, supervision, project administration. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors do not report any relevant conflict of interest.

References

1. Vos, T.; Abajobir, A.A.; Abate, K.H.; Abbafati, C.; Abbas, K.; Abd-Allah, F.; Abdulkader, R.S.; Abdulle, A.M.; Abeko, T.A.; Abera, S.F.; et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017, 390, 1211–1259. [CrossRef]
2. Kabbouche, M.A.; Powers, S.W.; Vockell, A.-L.B.; LeCates, S.L.; Ellinor, P.L.; Segers, A.; Manning, P.; Burdine, D.; Hershey, A.D. Outcome of a Multidisciplinary Approach to Pediatric Migraine at 1, 2, and 5 years. Headache 2005, 45, 1298–1303. [CrossRef] [PubMed]
3. Powers, S.W.; Patton, S.R.; Hommel, K.A.; Hershey, A.D. Quality of life in childhood migraines: Clinical impact and comparison to other chronic illnesses. Pediatrics 2003, 112, e1–e5. [CrossRef] [PubMed]
4. Qureshi, M.H.; Esper, G.J.; Bashir, F.F. When to Consider Prophylactic Antimigraine Therapy in Children with Migraine. Curr. Treat. Options Neurol. 2019, 21, 15. [CrossRef] [PubMed]
5. Kacperski, J.; Kabbouche, M.A.; O’Brien, H.L.; Weiderling, J.L. The optimal management of headaches in children and adolescents. Ther. Adv. Neurol. Disord. 2016, 9, 53–68. [CrossRef] [PubMed]
6. Hepp, Z.; Dödick, D.W.; Varon, S.F.; Gillard, P.; Hansen, R.N.; Devine, E.B. Adherence to oral migraine-preventive medications among patients with chronic migraine. Cephalalgia 2015, 35, 478–488. [CrossRef]
7. Bachur, R.; Monuteaux, M.C.; Neuman, M.I. A Comparison of Acute Treatment Regimens for Migraine in the Emergency Department. Pediatrics 2015, 135, 232–238. [CrossRef] [PubMed]
8. Richer, L.; Graham, L.; Klassen, T.; Rowe, B. Emergency Department Management of Acute Migraine in Children in Canada: A Practice Variation Study. Headache 2007, 47, 703–710. [CrossRef]
9. Klim, S.; Krieser, D.; Kelly, A. Sub-optimal treatment of paediatric migraine in an emergency department: An observational study. Emerg. Med. Australas. 2019, 31, 879–881. [CrossRef]
30. Tassorelli, C.; Grazzi, L.; De Tommaso, M.; Pierangeli, G.; Martelletti, P.; Rainero, I.; Dorlas, S.; Geppetti, P.; Ambrosini, A.; Sarchielli, P.; et al. Noninvasive vagus nerve stimulation as acute therapy for migraine. *Neurology* 2018, 91, e364–e373. [CrossRef]

31. Mitsikostas, D.D.; Rapoport, A.M. Chronic migraine prevention with non-invasive vagus nerve stimulation in a prospective pilot study (the event study): Report from the open-label phase. *Headache* 2014, 13, 279.

32. Lipman, J.J.; Miller, B.E.; Mays, K.S.; Miller, M.N.; North, W.C.; Byrne, W.L. Peak B endorphin concentration in cerebrospinal fluid: Reduced in chronic pain patients and increased during the placebo response. *Psychopharmacology* 1990, 102, 112–116. [CrossRef]

33. Benedetti, F.; Pollo, A.; Lopiano, L.; Lanotte, M.; Vighetti, S.; Rainero, I. Conscious Expectation and Unconscious Conditioning in Analgesic, Motor, and Hormonal Placebo/Nocebo Responses. *J. Neurosci.* 2003, 23, 4315–4323. [CrossRef]

© 2020 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).