EDUCATIONAL RESOURCE
Volume 8 Issue 4 2016
DOI: 10.5959/eimj.v8i4.460
ARTICLE INFO
Submitted: 13-08-2016
Accepted: 14-09-2016
Online: 30-12-2016

The Ethics of Managing Recurrent Respiratory Papillomatosis in Children: A Case Study

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To cite this article: Yusoff MRM, Mavinkurve M, Subramaniam S, Che Nik MA, Taib F, Hazama M, Suzina SAH. 2016. The ethics of managing recurrent respiratory papillomatosis in children: a case study. Education in Medicine Journal. 8(4):83–87. DOI: 10.5959/eimj.v8i4.460

To link to this article: http://dx.doi.org/10.5959/eimj.v8i4.460

ABSTRACT

Recurrent respiratory papillomatosis (RRP) is a rare cause of childhood stridor which typically presents before the age of five years and results from the vertical transmission of the human papilloma virus. Genotypes 11 and 6 are commonly implicated in RRP. Following vertical transmission, the human papilloma virus (HPV) causes overgrowth of the airway epithelium which causes partial airway obstruction and the symptoms of stridor. The mainstay management is surgical debridement of the papillomata but the recurrence rate subsequent to surgery is high, such that most children will require repeated surgical procedures at regular interval. Medical adjuvant therapy can be used, but data is limited and the medications are used on an off-label basis. This case highlights the ethical considerations that need to be made when using off-label medications in paediatric patients.

Keywords: *Off label medication, Respiratory papilomatosis, Evidence based medicine, Children*

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INTRODUCTION

Recurrent respiratory papillomatosis (RRP) is an infection of the respiratory tract epithelium due to the vertical transmission of human papilloma virus (HPV). The acquisition of HPV results in the overgrowth of the epithelial cells of the airway anywhere from the larynx to the bronchi. The typical presenting symptom is stridor which is detected before the age of four years. The mainstay therapy is surgical debridement of the papillomata but the success rate in inducing long-term remission is poor. Medical adjuvant therapies to complement surgical intervention include the use of intralesional cidofovir, or the use of Gardasil™ which is the quadrivalent HPV vaccine that was FDA approved in 2006. The medical therapy used in the management of RRP is based on low-level scientific evidence. As such, the medications are off-label. This raises important ethical issues for their use in the paediatric setting.

CASE

We discuss the case of a three year-old Malay boy, who is the only child of a non-consanguineous couple who presented with a week duration of stridor and hoarseness. The stridor was unresponsive to a trial of inhaled bronchodilators and inhaled corticosteroids. The symptom persisted for three weeks despite therapy, thus a decision to conduct laryngoscopy was made. On direct laryngoscopy multiple papillomatous warts were visualised at the vocal cords and the surrounding tissues. The histopathological examination confirmed a diagnosis of laryngeal papillomatosis. Serotyping could not be undertaken due to logistical issue. Surgical micro-debridement was conducted which resulted in resolution of the stridor at the immediate post-operative period. However, the patient experienced a recurrence of symptoms one to two months after the debridement. This warranted a repeat surgical procedure. Unfortunately, this patient required multiple episodes of surgical micro-debridement. To date, he has had 20 surgical de-bulking procedures. Due to frequent relapsing symptoms, he was referred to the paediatric team for consideration of adjuvant medical therapy such as Gardasil™ (1) and propranolol (2). Both of these options were trialed but with poor clinical effect. Escalation of therapy by using interferon-α or cidofovir was next attempted after a poor response with the initial medical intervention.

In his background, the child was born at term by spontaneous vaginal delivery with the birth weight of 3.8 kg. The mother denied the presence of condylomata at the time of delivery. All her viral serology was negative and her cervical swab only indicated growth of normal flora. She denied having had the HPV vaccine, but had completed the standard immunisation schedule according to the Expanded Programme of Immunization in Malaysia.

ETHICAL CASE DISCUSSION

This case raises ethical issues surrounding the decision to use off-label medications in the treatment of rare conditions seen in paediatric. The off-label medications in this case are Gardasil™, the quadrivalent HPV vaccine for HPV serotypes 6, 11, 16, 18 and propranolol, a beta-blocker. Their clinical use was based on Level 5 evidence (3).

Off-label prescriptions are those that are used in a manner which is either not specified in the medication insert or is not an accepted mode of standard treatment (4). In addition, evidence regarding safety and efficacy may be lacking thus making rational drug choices difficult.

Interestingly, in paediatrics, more than 50% of prescribed medications are used off-label. This is because most medications lack efficacy and safety data in childhood cohorts. In spite of it being common practice among paediatricians, the practice itself must be conducted in a judicious manner. The American Academy of Paediatrics has issued a statement in 2014, which reminded the clinicians that considerable thought should be given about risks and benefits as well as evidence to support the use of off-label medications in children. This is also endorsed by the Malaysian Paediatric Association (http://mpaweb.org.my/).

The decision to use off-label medications should be guided by several factors. Firstly, clinical assessment of the patient should be conducted to determine if the medication is truly appropriate for the case (5). Secondly, the importance of basic medical ethics principles should be applied to the decision making process to ensure that the best care (beneficence) is provided to the patient with no harm incurred (non-maleficence) when using an off-label product. Finally, additional ethical principles such as autonomy and justice will also need to be factored into the decision making process

prior to commencing the patient on treatment.

Beneficence

Beneficence is the ethical principle of "doing good" for the benefit of the patient. In order to do so, the clinician needs to weigh the benefits of the off-label medication and determine if it out-weighs the risks associated with it. Medical alternatives to the off-label treatment whose safety and therapeutic profiles have been studied should be heavily considered before using an off-label medication. In the current case, the child has undergone several surgical procedures to his airway each with their own risks, including the risk of the anaesthetic procedure itself. The mainstay treatment is surgical micro-debridement, by using lasers such as CO_2, potassium titanyl phosphate (KTP) and pulsed dye (6). These procedures are associated with risks (7) as well as the risks associated with the anaesthesia. However, in this case the surgery had failed to induce long term relief of the stridor and the fact that each surgical procedure is associated with potential anaesthetic risk and preservation of an acceptable quality of voice, prior to using the off-label drug (8). On this note, the off-label medications were considered to provide medical therapy which benefitted the patient. The difficulty arises when one needs to consider if the off-label therapy that is based on low-level evidence be deemed safe and effective? Furthermore, if the trial of therapy with the off-label medication fails to induce a longer remission period, then is it fair to subject this child to another course of an off-label drug again? These are all issues that encroach on another ethical principle of non-maleficence.

Non-maleficence

Non-maleficence refers to the clinician's duty to deliver care that "does no harm" to the patient. Relying on anecdotal case report to direct clinical management should raise the question as to whether the clinician and the patient alike have enough evidence and understanding on the short and long-term side effects of the off-label drug, and to be able to make an informed decision as to whether this treatment will "cause harm" or not. In this case, given that the standard treatment had failed, and with no other treatment options, off-label medications had to be considered. Furthermore, the with-holding of the off-label medication could potentially have resulted in severe airway obstruction, which is an adverse outcome for the patient, in addition to causing anxiety for the family.

Autonomy

Another ethical principle which this case alludes to is autonomy. Autonomy refers to the patient's right to accept or refuse medical treatment. In paediatrics, autonomy is exercised by the legal guardians on behalf of the patient. However, in order to exercise autonomy, the patient and his carers must be duly informed about the risks and benefits of the therapy. Using off-label medications, for which safety and efficacy data may be limited, will compromise the clinician's ability to give appropriate information to the patient.

Justice

Justice is another fundamental medical ethical principle whereby patient treatment should be allocated as fairly as possible. The cost of Gardasil™ is approximately US$375. In this case, the question arises whether these funds could be more appropriately used by the public health system for other therapies that have proven benefit. Even other experimental medications, for instance interferon-α, may take up to exorbitant cost for the family to bear. Is it justifiable to subject the family to this experimental practice when a favourable outcome is questionable?

In paediatrics, the clinician must uphold the ethical principles for the child, a vulnerable patient. It must be remembered that it is the

child, not the family members, that has the right to treatment and that all therapeutic efforts should be made in the interest of the child. Recognition of this duty should be made clear from the start. In practice, it is likely that an assessment of the scientific evidence regarding the off-label medication is required to weigh the benefits and risks and thus guide patient's therapy. In addition, informing the patient and family that the treatment choice is based on limited evidence and why off-label medication has to be used, will enable the parents make an informed decision. The ethical concepts of beneficence, non-maleficence and autonomy all need to be considered in order to guard the interests of the paediatric patient. In addition to addressing these ethical principles, the clinician also has the obligation to report the beneficial or harmful effects as well as the clinical outcome of the off-label medication, so that other clinicians can make informed decisions regarding its use. Clinicians also bear the obligation of advocating more researches in paediatric medications, so that the evidence gap can be filled. This will allow children to avail to medications that are based on high-level evidence. Finally, it is important to recognise that though clinicians are required to practice their skills with compassion and in an ethical manner, but this must do so within the boundaries of the legal system. A statement put forth by the American Academy of Paediatrics reminds clinicians that the use of off-label medications "… should be done in good faith, in the best interest of the patient and without fraudulent intent" (9).

Parental Screening

Another ethical issue that arises in this case pertains to parental screening. HPV is acquired by the baby whilst in-transit through the birth canal during delivery. Thus, the question regarding screening of the parents becomes an issue since this could be transmitted to future babies. In this case, the mother denied the presence of genital condylomata and high risk behaviour. Nonetheless, screening both parents for HPV enables genotyping which can then be used to predict future risk of malignancy, risk of transmission in future pregnancies and the risk of cervical cancer to the mother. Screening for other sexual transmitted diseases in parents can be a challenging task due to the stigma and the need to keep the information confidential (10). There are other ethical dilemmas that arise: whether to reveal the information to the patient with or without the partner present, and whether to explore sexual history and refer to the infectious diseases team while preserving confidentiality.

In Malaysia, HPV is the leading cause of cervical cancer, with more than 80% of cervical cytological specimens of cervical cancer being positive for HPV 16 or 18. This indicates that the HPV vaccination becomes a vital consideration in the prevention of cervical cancer in women. Following the vertical transmission of HPV to the newborn, the treatment of RRP is limited to surgery at the present time. The use of medications is guided by low-grade evidence which is clearly complicated by several ethical issues. Future research should focus on developing a well-designed clinical trials to determine if adjuvant medical therapy has a role in the treatment of RRP (11).

CONCLUSION

The management of rare medical conditions that are incurable is not straight forward. As illustrated in this case, lack of evidence for treatment decisions results in several ethical issues. Though the physician may be taking "the road which is not usually taken" (12) in terms of medical treatment, when using off-label therapy, reliance on good clinical judgement, consideration of basic medical ethics and putting the medical interests of the patient first will ensure that the treatment is ethical, personalised and accountable.

ACKNOWLEDGEMENTS

The authors would like to express sincere gratitude to the involved physician and parents in the management of this condition.

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