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MALIGNANT HYPERTHERMIA: HISTORY OR REALITY

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ЗЛОКАЧЕСТВЕННАЯ ГИПЕРТЕРМИЯ: МИФ ИЛИ РЕАЛЬНОСТЬ

Актуальность. Одним из факторов риска анестезиологической помощи является развитие такого осложнения как злокачественная гипертермия (ЗГ). Этот феномен введен в медицинскую практику с 1960 г. Смертность от ЗГ значительно снизилась с пониманием патофизиологических процессов, происходящих в организме и появлением специфической терапии, но летальные исходы случаются до сих пор при фульминантном течении злокачественной гипертермии.

Описание клинического случая. У пациента, которому оказывалась анестезиологическая помощь с пропофолом, изофлюраном и атракурия бессилатом для проведения оперативного вмешательства в объеме аппендэктомии, развилась ЗГ. Пациент умер от развившейся полиорганной недостаточности при отсутствии дантролена.

Выводы. Криз ЗГ является редким осложнением с серьезным риском летального исхода для восприимчивых лиц. Для того чтобы сохранить смертность низкой, необходимо проводить подробный предоперационный осмотр и сбор анамнеза, адекватный интраоперационный мониторинг, иметь в наличии достаточный запас дантролена и тщательно подготавливать анестезиологов и коллектив в любом медицинском учреждении, где проводится общая анестезия.

Ключевые слова: анестезия, злокачественная гипертермия, контрактурный тест, дантролен.

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Introduction. Malignant Hyperthermia (MH) is known as an anaesthetic risk since 1960. Morbidity has decreased remarkably with better understanding of the pathophysiology and availability of a specific treatment, but still patients are dying of a fulminant MH crisis.

Case Presentation. We report a male patient undergoing general anaesthesia with propofol, isoflurane and atracurium for appendectomy developing Malignant Hyperthermia. The boy dies of multiple organ failure in unavailability of dantrolene. As

the parents could not afford the far travel to a MH laboratory to undergo an IVCT (In vitro contracture test) we did a genetic analysis of their blood. The results of mutation screening showed no mutations in the father and a mutation in exon 40: 6635 T>C Val-2212-Alnine. This mutation is not accepted as causative by the European Malignant Hyperthermia Organisation .

Conclusions. Crisis of MH is a rare event with a serious risk of lethal outcome for susceptible individuals. In order to keep mortality low, meticulous preoperative evaluation of patient medical history, adequate intraoperative monitoring, availability of a sufficient stock of dantrolene and thorough training of anesthetists and theatre staff need to be provided by any institution delivering general anaesthesia.

Key words: Anesthesia; Malignant Hyperthermia; In vitro contracture test; dantrolene

Introduction

Malignant Hyperthermia (MH) has been known as an anaesthetic risk since 1960. Since then the knowledge of MH pathophysiology has increased markedly and specific therapeutic treatment has become available. Malignant hyperthermia (MH) is a hypermetabolic, pharmacogenetic myopathy associated with high mortality. With the introduction of dantrolene as a specific treatment agent, the application of a standardized monitoring on patients and by improved training of anaesthesiologists, the mortality of MH could be reduced from 80% in the sixties and seventies of the past century to below 5% today. In reality there are still patients dying of MH. The nature of MH has recently been elucidated, but it still remains difficult to predict and prevent a potentially lethal event of Malignant Hyperthermia. By some anaesthesiologists MH might be viewed as a historic disease only, as the use of triggering drugs like volatile anaesthetics and succinylcholine has decreased. But the case we report emphasizes the stringent necessity of alertness to any sign of incipient MH in any non-triggerfree anaesthesia we perform in our daily operation theatre routine.

Case Presentation

At 3 p. m. in September 2006 a 16 years old adolescent is admitted to a hospital in an eastern European capital to undergo surgery for acute appendicitis. His medical history and laboratory results are unremarkable.

Anaesthesia is inducted with fentanyl, succinylcholine and disoprivan, maintenance of anaesthesia is performed with isoflurane, fentanyl and atracurium. Except for tachycardia of 100 bpm no other abnormalities are observed initially.

About 7 p. m. at the end of the operation the heart rate increases to more than 140 bpm, the axillary temperature is 39.4 °C and subsequently rises to over 42 °C. Antipyretic treatment is initialized and the patient remains intubated and ventilated. A Malignant Hyperthermia crisis is considered by the treating anaesthesiologists. They start straight away with a treatment according to the protocol of MHAUS (Malignant Hyperthermia Association of the United States). Unfortunately Dantrolene® is not available.

Laboratory results:

7:50 p. m.: Potassium — 5.98 mmol/l; $PaCO_2$ — 219 mmHg; pH — 6.8

8:13 p. m. : Creatinkinase 4268 U/L (normal value 47–222 U/l); Laktat-Dehydrogenase 860 U/L (normal value < 250 U/l); Creatinine 166 μmol/l (normal value 62–106 μmol/l)

8:50 p. m.: Platelets 130,000/мl (normal value 140,000–440,000/μl)

9:45 p. m: Platelets 60,000/мl

10:30 p. m.: Potassium 7.01 mmol/l

About 8:30 p.m. hypercoagulability and severe hemorrhage set in. The initial treatment is expanded by delivery of H_2-Antagonists, fresh frozen plasma and general cooling. In the next hour the patient develops anuria and a lung edema. In hope to stop the hemorrhage recombinant factor 7 (Novoseven®) is substituted.

About 10:00 p. m. conduction of hemodialysis is considered, but despite all efforts of treatment the young patient dies at 0:30 p. m. of multiple organ failure.

The parents of the boy are distraught about the sudden death of their child and search internationally for advice and help.

As the parents could not afford the far travel to a MH laboratory to undergo an IVCT (In vitro contracture test) we did a genetic analysis of their blood. The results of mutation screening showed no mutations in the father and a mutation in exon 40: 6635 T>C Val-2212-Alnine in the mother. This is missense point mutation causing a replacement of the nucleotide Valine by the nucleotide Alanine. This mutation is not yet accepted as causative by the European Malignant Hyperthermia Organisation.

Conclusions

Death from MH crisis can still occur, even in the best of hands. If this worst case occurs, it will have a dramatic, traumatic effect on the entire medical staff, demanding a long recovery time of the adverse event.

In 2013 Wochna reports the death of a 4 year old boy undergoing dental treatment in general anaesthesia. In the same year Lavezzi reports the death of a 6 years old boy in the US. Postmortem genetic analysis presented a novel RYR1 receptor variant. IVCT (*in vitro* contracture test) of the father resulted in susceptibility to MH (MHS) and central core disease was diagnosed histologically. Genetic analysis revealed the same RYR1 variant as the boy.

Reviewing the publications of this century more similar case reports are to be found.

In 2004, Yip reports a mortality of MH in Taiwan as high as 28.6% due to the lack of intraoperative monitoring and availability of dantrolene. By the interviewed hospitals 66% routinely used pulse oxymeter, 77% $ETCO_2$ concentration monitoring, but only 19.7% a continuous body temperature measurement. 34.9% store six ore more vials of dantrolene for immediate use, the rest of 65.1% does not have any stock of dantrolene.

Remarkably in 2002 only 35.3% of hospitals in Japan used capnography and only 29.7% continuous body temperature measurement. 66% have 6 or more vials of dantrolene in stock and only 33% in the operating room.

Therefore MH claims lives throughout the world in spite of optimal treatment even in our millennium.

The increasing use of total intravenous anaesthesia (TIVA) using non-triggering agents in the Western hemisphere seems to make a crisis of MH an even rarer event. However an increasing number of MH events have been reported. Awareness of MH symptoms among anaesthetists and theatre staff may be reduced and potentially lead to an increased risk of a too late or undiagnosed event. Due to the autosomal-dominant inheritance, prevalence of MH can be estimated up to 1:3000. According to the pooled data of the German MH laboratories in 1997 a prevalence of at least 1:60,000 to 1:80,000 in Germany was estimated. Analyzing the residency of the MH families an increased regional prevalence in the areas of the MH laboratories was determined.

Even though an MH crisis may develop at first exposure to anesthesia with triggering agents (inhalation agents: halothane, isoflurane, sevoflurane, desflurane, depolarizing muscle relaxant: succinylcholine) on average, patients require three anesthetics before triggering. Reactions develop more frequently in males than females (2:1). All ethnic groups are affected, in all parts of the world. The highest incidence is in young people, it has been found that children under 15 years age comprised 52.1% of all reactions.

The incidence of MH episodes during general anaesthesia is between 1:10,000 and 1:250,000 anaesthetics. An uneventful general anaesthesia is no predictor for the future, some patients trigger after multiple anaesthetics. MH can develop at any time during anaesthesia as well as in the early postoperative period. The progression of the syndrome may be rapid and dramatic, especially after administration of succinylcholine in combi-

nation with a volatile anaesthetic, or more slowly with a manifestation after several hours after induction of anaesthesia.

It is impossible to diagnose MH susceptibility without either exposure to trigger anaesthetics or by specific testing by IVCT according to the guidelines of European Malignant Hyperthermia Group, or the guidelines of the North American Malignant Hyperthermia Group. IVCT remains the current "gold standard" of MH diagnosis. Genetical testing supports the IVCT in family screening but is not a substitute for IVCT. Nevertheless a clinical grading scale developed by Larach can be a helpful tool to predict the probability of a MH susceptibility.

A minority of muscular diseases are strongly related with a predisposition for Malignant Hyperthermia. The majority of patients with Central Core Disease (CCD), an inherited myopathy characterized by muscle weakness, are susceptible to MH. Multi-minicore Disease (MmD), central nuclear myopathy and King-Denborough syndrome also predispose to episodes of MH. Nevertheless a variety of patients with muscular diseases develop MH like symptoms like masseter spasm and muscle rigidity as a reaction on delivery of succinylcholine. In patients with any kind of muscular disorder particularly muscular dystrophies like hypokalemic periodic paralysis, CCD, Duchenne or Becker conduction a triggerfree anaesthesia is highly recommended.

Dantrolene sodium is the cornerstone of a successful treatment of any MH episode. This specific antagonist should be available wherever general anaesthesia is administered. It is unavailable in many institutions in Eastern countries and developing countries due to its cost, leading to an increased risk of MH fatalities in these areas.

In order to minimalize the death rate of MH events the following principal aims are to be painstakingly observed:

Preoperative Evaluation

An extensive preoperative evaluation of the patient's and families medical history concerning muscular diseases, muscle cramping on strong exercise, adverse events during previous anaesthetics, deaths of anaesthesia needs to be conducted. The use of the clinical grading scale by Larach and colleagues may be a helpful tool for clinical assessment of the significance of a previous adverse event. Elevated CK measurement is no clear evidence of MH susceptibility, but many MH susceptible patients present with a raised CK.

Intraoperative monitoring

The principal clinical features of MH are masseter spasm, muscle rigidity, tachycardia, unexplained elevation, hyperkalemia, acidosis and hyperthermia. Since the order and onset of the signs follow a variability the clinical diagnosis may be fairly difficult. Such being the case, any patient under general anaesthesia should be monitored with measurement of $ETCO_2$ concentration and core temperature monitoring. Early recognition of MH symptoms and routine use of core temperature monitoring are essential in minimizing mortality and morbidity from MH.

Dantrolene

Dantrolene sodium is the only medication for the treatment of MH events. It binds to a specific site on the RYR1 protein. Since the introduction of the drug in 1979 mortality of MH was reduced to 5% due to the application of the substance in MH events. For North America a mortality of 1.4% is reported.

There are two preparations of dantrolene available: Dantrium® and Ryanodex®.

The original preparation called Dantrium® is available in 20 mg vials of the lyophilized drug, which must be reconstituted in 60 ml of sterile water before administration. Dantrium® is poorly soluble, so the preparation of an adequate initial dose of 2.5 mg/kg body weight, equating 8–10 ampoules for an average adult male, is time consuming and

needs additional staff. In 2014 a novel preparation of dantrolene sodium named Ryanodex® was approved by the FDA. It has a higher solubility, one ampoule contains 250 mg dantrolene, and requires 5 ml of sterile water only for restitution. Therefore initial treatment can be achieved now with administration of one ampoule. The efficiency of Ryanodex® is the same as Dantrium®. There is no upper dose of dantrolene, it should be titrated following to tachycardia and hypercarbia. An administration of dose higher than 10 mg/kg body weight without result needs a reconsideration of the diagnosis MH. The immediate availability of more than six vials of Dantrium® in the operation theatre and its prompt administration in less than 30 minutes must be guaranteed in any institution delivering non-triggerfree general anaesthesia.

Training of Anaesthetists and Theatre Staff

Since MH crises are very rare events, medical staff needs training on treating an MH crisis in regular intervals. For further training on MH crisis the websites of MHANZ and MHA US provide with the free use of task cards, a management poster and educational material. The EMHG published guidelines for recognizing and managing a Malignant hyperthermia in 2010 in the British Journal of Anaesthesia, also to be found on the EMHG website. Due to the fact that the outcome of a patient with a MH crisis depends severely on promptness of diagnosis and administration of treatment every institution needs to dispose of a alert and well trained theatre staff.

Genetic diagnostics

Today sequencing of nearly 100 per cent of the RYR-1-gene is feasible. A clear clinical case of Malignant Hyperthermia given, MH diagnostic through genetic diagnostics can be conducted. The frequency of mutations seems to vary strongly in different regions all over the continents. The mutation in the above described case may be frequent in Eastern Europe but not in Western Europe. This could be an explanation why it has not been found in extensive MH-screenings in Germany, Italy and the US. Extensive genetic diagnostics in Eastern Europe may lead to new results about the frequency of some already described mutations.

Malignant Hyperthermia is a reality all over the world, even though the mortality rate has been reduced remarkably. For susceptible individuals remains a serious risk of a crisis if undergoing general anaesthesia using volatile anaesthetics and/or depolarizing muscle relaxants.

The work of certified MH laboratories is of utmost importance, not only as diagnostic facilities but also as centre for disseminating expert knowledge and advice.

REFERENCES

1. *Denborough M.* Anaesthetic deaths in a family / M. Denborough, R. Lovell // Lancet. – 1960. – N 2. – P. 45.

2. *Emergency* Treatment for An Acute MH Event [Electronic resource]. – Access mode : http://www.mhaus.org/healthcare-professionals/managing-a-crisis

3. *Mutations* in RYR1 [Electronic resource]. – Access mode : https://emhg.org/genetics/mutations-in-ryr1/

4. *Sudden* death due to malignant hyperthermia during general anesthesia / K. Wochna, A. P. Jurczyk, W. Krajewski, J. Berent // Arch Med Sadowej Kryminol. – 2013. – N 63 (1). – P. 11–4; 7–10.

5. *Case* report: Death in the emergency department: an unrecognized awake malignant hyperthermia-like reaction in a six-year-old / W. A. Lavezzi, J. F. Capacchione, S. M. Muldoon [et al.] // Anesth Analg. – 2013. – N 116 (2). – P. 420–423.

6. *A fulminant* Malignant Hyperthermia Episode in a Patient with ryanodine receptor Gene Mutation p. Tyr522Ser / T. Girard, M. Suhner, S. Levano [et al.] // Anesthesia&Analgesia. – 2008. – N 107 (6). – P. 1953–1955.

7. *A survey* for prevention and treatment of malignant hyperthermia in Taiwan / W. H. Yip, C. L. Mingi, S. J. Ooi [et al.] // Acta Anaesthesiol Taiwan. – 2004. – Vol. 42 (3). – P. 147–151.

8. *Trends* and outcome of Malignant Hyperthermia on the United States, 2000 to 2005 / E. B. Rosero, A. O. Adesanya, C. H. Timaman [et al.] // Anesthesiology. – 2009. – N 110. – P. 89–94.

9. *Regional* distribution of predisposition to maligant hyperthermia in Germany: date in 1997 / E. Hartung, M. Anetseder, D. Olthoff [et al.] // Anasthesiol Intensivmed Notfallmed Schmerzther. – 1998. – N 33 (4). – P. 238.

10. *Malignant* hyperthermia in Canada: characteristics of index anesthetics in 129 malignant hyperthermia susceptible probands / S. Riazi, M. G. Larach, C. Hu [et al.] // Anesth Analg. – 2014. – N 118 (2). – P. 381–387.

11. *A protocol* for the investigation of malignant hyperpyrexia (MH) susceptibility. The European Malignant Hyperpyrexia Group / British Journal of Anaesthesia. – 1984. – N 56 (11). – P. 1267–1269.

12. *Prediction* of malignant hyperthermia susceptibility in low-risk subjects. An epidemiologic investigation of caffeine halothane contracture responses. The North American Malignant Hyperthermia Registry / M. G. Larach, J. R. Landis, J. S. Bunn [et al.] // Anesthesiology. – 1992. – N 76 (1). – P. 16–27.

13. *Criteria* for gene mutations to be used in genetic testing of Malignant Hyperthermia susceptibility. – Available at : emhg.org/fileadmin/EMHG/redaktion/Guidelines/Mutationcriteria2003. pdf

14. *A clinical* grading scale to predict malignant hyperthermia susceptibility / M. G. Larach, A. R. Localio, G. C. Allen [et al.] // Anesthesiology. – 1994. – N 80 (4). – P. 771–779.

15. *Muscle* biopsy and in vitro contracture test in subjects with idiopathic HyperCKemia / A. Malandrini, A. Orrico, C. Gaudiano [et al.] // Anesthesiology. – 2008. – N 109 (4). – P. 625–628.

16. *Malignant* hyperthermia deaths related to inadequate temperature monitoring, 2007–2012: a report from the North American malignant hyperthermia registry of the malignant hyperthermia association of the United States / M. G. Larach, B. W. Brandom, G. C. Allen [et al.] // Anesth Analg. – 2014. – N 119 (6). – P. 1359–1366.

17. *Identification* of a dantrolene-binding sequence on the skeletal muscle ryanodine receptor / K. Paul-Pletzer, T. Yamamoto, M. B. Bhat [et al.] // J Biol Chem. – 2002. – N 277 (38). – P. 34918–34923.

18. *Malignant* hyperthermia: a review / H. Rosenberg, N. Pollock, A. Schiemann [et al.] // Orphanet J Rare Dis. – 2015. – N 10. – P. 93.

19. *Malignant* Hyperthermia Australia and New Zealand. – Available at : http://www.anaesthesia.mh.org.au/mh-resource-kit/w1/i1002692/.

20. *Malignant* Hyperthermia Association of the USA. – Available at : http://www.mhaus.org.

21. *Recognizing* and managing a malignant hyperthermia crisis: guidelines from the European Malignant Hyperthermia Group / K. P. E. Glahn, F. R. Ellis, P. J. Halsall [et al.] // Br J Anaesth. – 2010. – N 105 (4). – P. 417–420.

REFERENCES

1. Denborough M., Lovell R. Anaesthetic deaths in a family. *Lancet* 1960; 2: 45.

2. Emergency Treatment for An Acute MH Event. Available at: http://www.mhaus.org/healthcare-professionals/managing-a-crisis

3. Mutations in RYR1. Available at: https://emhg.org/genetics/mutations-in-ryr1/

4. Wochna K., Jurczyk A.P., Krajewski W., Berent J. Sudden death due to malignant hyperthermia during general anesthesia. *Arch Med Sadowej Kryminol*, 2013; 63 (1): 11-4, 7-10.

5. Lavezzi W.A., Capacchione J.F., Muldoon S.M., Sambuughin N., Bina S., Steele D., Brandom B.W. Case report: Death in the emergency department: an unrecognized awake malignant hyperthermia-like reaction in a six-year-old. *Anesth Analg*, 2013; 116 (2): 420-423.

6. Girard T., Suhner M., Levano S., Singer M., Zollinger A., Hofer C.K. A fulminant Malignant Hyperthermia Episode in a Patient with ryanodine receptor Gene Mutation p. Tyr522Ser. *Anesthesia&Analgesia*, 2008; 107; 6: 1953-1955.

7. Yip W.H., Mingi C.L., Ooi S.J., Chen S.C., Chiang Y.Y. A survey for prevention and treatment of malignant hyperthermia in Taiwan. *Acta Anaesthesiol Taiwan*, 2004; 42 (3): 147-151.

8. Rosero E.B., Adesanya A.O., Timaman C.H., Joshi G.P. Trends and outcome of Malignant Hyperthermia on the United States, 2000 to 2005. *Anesthesiology*, 2009; 110: 89-94.

9. Hartung E., Anetseder M., Olthoff D., Deutrich C., Lehmann-Horn F., Baur C., Mortier W., Tzanova I., Doetsch S., Quasthoff S., Hofmann M., Schwefler B., Jantzen J.P., Wappler F., Scholz J. Regional distribution of predisposition to maligant hyperthermia in Germany: date in 1997. *Anasthesiol Intensivmed Notfallmed Schmerzther* 1998; 33 (4): 238.

10. Riazi S., Larach M.G., Hu C., Wijeysundera D., Massey C., Kraeva N. Malignant hyperthermia in Canada: characteristics of index anesthetics in 129 malignant hyperthermia susceptible probands. *Anesth Analg*, 2014; 118 (2): 381-387.

11. A protocol for the investigation of malignant hyperpyrexia (MH) susceptibility. The European Malignant Hyperpyrexia Group. *British Journal of Anaesthesi*a 1984; 56 (11): 1267-1269.

12. Larach M.G., Landis J.R., Bunn J.S., Diaz M. Prediction of malignant hyperthermia susceptibility in low-risk subjects. An epidemiologic investigation of caffeine halothane contracture responses. The North American Malignant Hyperthermia Registry. *Anesthesiology* 1992; 76 (1): 16-27.

13. Criteria for gene mutations to be used in genetic testing of Malignant Hyperthermia susceptibility. Available at: emhg.org/fileadmin/EMHG/redaktion/Guidelines/Mutationcriteria2003.pdf

14. Larach M.G., Localio A.R., Allen G.C., Denborough M.A., Ellis F.R., Gronert G.A., Kaplan R.F., Muldoon S.M., Nelson Th.E., Ørding H., Rosenberg H., Waud B.E., Wedel D.J. A clinical grading scale to predict malignant hyperthermia susceptibility. *Anesthesiology* 1994; 80 (4): 771-779.

15. Malandrini A., Orrico A., Gaudiano C., Gambelli S., Galli L., Berti G., Tegazzin V., Dotti M.T., Federico A., Sorrentino V. Muscle biopsy and in vitro contracture test in subjects with idiopathic HyperCKemia. *Anesthesiology*, 2008; 109 (4): 625-628.

16. Larach M.G., Brandom B.W., Allen G.C., Gronert G.A., Lehman E.B. Malignant hyperthermia deaths related to inadequate temperature monitoring, 2007–2012: a report from the North American malignant hyperthermia registry of the malignant hyperthermia association of the United States. *Anesth Analg*. 2014; 119 (6): 1359-1366.

17. Paul-Pletzer K., Yamamoto T., Bhat M.B., Ma J., Ikemoto N., Jimenez L.S., Morimoto H., Williams P.G., Parness J. Identification of a dantrolene-binding sequence on the skeletal muscle ryanodine receptor. *J Biol Chem*, 2002; 277 (38): 34918-34923.

18. Rosenberg H., Pollock N., Schiemann A., Bulger T., Stowell K. Malignant hyperthermia: a review. *Orphanet J Rare Dis*, 2015; 10: 93.

19. Malignant Hyperthermia Australia and New Zealand. Available at: http://www.anaesthesia.mh.org. au/mh-resource-kit/w1/i1002692/

20. Malignant Hyperthermia Association of the USA. Available at: http://www.mhaus.org.

21. Glahn K.P.E., Ellis F.R., Halsall P.J., Müller C.R., Snoeck M.M.J, Urwyler A., Wappler F. Recognizing and managing a malignant hyperthermia crisis: guidelines from the European Malignant Hyperthermia Group. *Br J Anaesth*, 2010; 105 (4): 417-420.

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