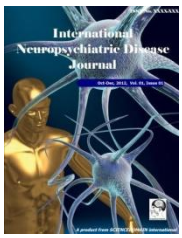

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Possible Effect of COMTVal158Met Polymorphism on the Association between Childhood Maltreatment and Externalizing Behavior: A Preliminary Study

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Over the course of the past decades, studies on child maltreatment have increasingly adopted multiple levels of analysis (particularly by the inclusion of genetics factors) on the basis of the variability in children's responses to stressful life events. This is a preliminary study on the effects of child maltreatment in a sample of adolescents according to this perspective.
Study Design: Case-control study.
Methodology: We investigated the moderating effect of COMT Val158Met polymorphism onthe association of child maltreatment with a range of externalizing behavior - assessed by the Child Behavior Check List/6-18 scale - in a sample composed of 52 maltreated children and adolescents and 90 healthy controls aged 10-

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18. Maltreatment was recorded on the basis of the presence/absence of physical contact.
Results: COMT Val158Met polymorphism interacts with physical contact abuse to influence externalizing behavior (p=.04), with both genetic (p=.03) and environmental risk factor (p=.003) having a significant main effect. Similar results were found considering the rule-breaking component of externalizing behavior, and the main effect of maltreatment was highly significant in all analyses performed.
Conclusion: This preliminary study supports the hypothesis that the variability in children's responses to maltreatment might be partially explained by individual genetic differences. Considering the presence of physical contact as a risk factor we could explain inconsistence of findings in literature on GxE in maltreatment.

Keywords: Externalizing behavior; COMT; childhood maltreatment; gene x environment interaction; physical abuse.

1. INTRODUCTION

Child abuse and neglect consists of any act of commission or omission by a parent or other caregiver that results in harm or potential for harm, to a child (0-18 years of age) even if the harm is unintentional [1]. It is a pervasive social problem that in Italy, affects a child out of a hundred [2] and whose medical and psychiatric consequences are largely recognized.

Many factors affect the consequences of child abuse and neglect, i.e. the age and the developmental status of the child when the abuse occurred, the severity, the frequency, the duration of maltreatment and the relationship between child and perpetrator. Many studies focused their attention on the effects of different kinds of abuse, neglect, emotional maltreatment, physical abuse and sexual abuse on different possible outcomes in terms of psychopathology. Although their results underline that not all abused children develop difficulties, there is a strong association between child maltreatment and the child's immediate and long-term psychopathological consequences [3-9]. According to social learning theory, numerous studies indicate conduct disorder, antisocial personality symptoms and aggressive behavior as consequences of maltreatment during early childhood [10-12]. Epidemiological data show that in the general population externalizing disorders occur with rates ranging approximately between 1% and 7% in children [13-16] while, among maltreated children, the prevalence varies between 23% and 56% [17-19]. Moreover, many studies have found a strong association between internalizing behavior and emotional abuse and neglect while sexual and physical abuse were closely associated with externalizing behavior [20-25].

According to recent research, which focused its attention on interactions between genes and environment (GxE) in the development of psychopathology [26-29], studies on child maltreatment have increasingly adopted multiple levels of analysis over the course of the past decades [30-32]. Clinical evidence underlines that not all subjects who are exposed to maltreatment develop psychopathological symptoms [33,34] and in a GxE perspective, it may be that these differences depend on genetic factors.

Among the biological mechanisms, the enzyme catechol-O-methyltransferase (COMT) plays a critical role in the metabolic degradation of synaptic dopamine and norepinephrine [35], neurotransmitters known to influence human cognition and behavior [36]. One of the features which render the dopamine system in the pre-frontal cortex different from other

brain regions is the significantly lower concentration of the dopamine transporter protein [37]. Such relative lack of dopamine transporter makes the pre-frontal cortex more dependent on other mechanisms, like the catechol-O-methyltransferase (COMT) enzyme, to terminate the action of released dopamine. Consistent with this view, the COMT enzyme accounts for more than 60% of dopamine degradation in the pre-frontal cortex, but for less than 15% of dopamine degradation in the striatum [38]. As a consequence, variations within the COMT gene, which encodes for the COMT enzyme, would be expected to affect the pre-frontal cortex's function much more dramatically than other brain regions (such as the striatum), the function of which could be relatively unaffected by the action of this enzyme. The COMT gene (located within the q11 region of chromosome 22) contains a single G-to-A base-pair missense variant. This polymorphism translates into a substitution of methionine for valine at codon 158 (Val158Met), with the enzyme containing Met158 having one-third to one-fourth of the activity of the Val158 enzyme [39] in degrading dopamine, epinephrine and norepinephrine.

A tonic-phasic dopamine hypothesis about the relationship between COMT and behavior was developed by Bilder, Volavka, Lachman and Grace [40]. They postulated that Met-carriers are characterized by increased levels of dopamine in the prefrontal region and that levels lead to increased high-frequency, low-amplitude tonic dopamine firing. This affords enhanced stability of cortical activation states and as a consequence, leads to the excessive rigidity that characterizes some externalizing symptoms. Excessive cognitive rigidity may impede the ability to smoothly transition to other cognitive states, resulting in abrupt “jumps” in activation states – including impulsive acts of aggression. Several studies support Blinder's hypothesis by reporting an association between externalizing behaviors and Met-allele, both in adult human [41-43] and animal samples [44,45] suggesting that the disadvantage of excessively stable activation states in the prefrontal region caused by excesses of tonic dopamine is a more difficult transition to a new activation state (and a new corrispondent behavior). However, the role of the Val158Met polymorphism in childhood and adolescents is still unclear with some studies reporting the Met allele [46] and others reporting Val allele [47] as risk factors for increased externalizing behavior.

Studies on maltreated subjects confirm the association between COMT and psychopathological traits but again, without agreement on the allele to be considered at risk. For example, Vinkers et al. [48] found that Val-homozygous individuals displayed increased psychotic experiences after exposure to cannabis use and childhood maltreatment compared to Met-heterozygous and Met-homozygous individuals. Also Perroud et al. [49] studied a sample of suicide attempters maltreated during childhood and they identified the Val allele as the risk variant of the COMT for anger traits. On the contrary, Wagner, et al. [50] found higher levels of impulsive aggression in borderline patients abused in infancy when they were homozygous for the Met allele.

Based on reported existing literature, i.e. on the hypothesis that the COMT genotype can moderate the influence of childhood maltreatment on neural systems implicated in externalizing behavior, we tested whether externalizing behavior would be predicted by an interaction between a gene (COMT) and an environment (maltreatment) in a clinical population sample of maltreated subjects with a control group made up of general population adolescents. A specific feature of our hypothesis was that COMT genotype contributes to the determination of externalizing behavior in different ways according to the presence (or not) of physical contact in the type of maltreatment experienced. This approach is based on data suggesting a stronger link between externalizing symptoms and physical contact forms of abuse [24,25].

2. MATERIALS AND METHODS

2.1 Subjects

Fifty-two maltreated subjects (30 male and 22 female; mean age 15.32 ± 1.55 years; age range: 13 to 18 years) were recruited over a 24-month period from the Children's Welcome Centre of our Scientific Institute, located in the urban area of Ostuni (Italy). Inclusion criteria for all participants were ages 10 to 18 and experiences of maltreatment in early childhood. Subjects were excluded if a genetic, prenatal or perinatal disorder was present.

The control group was composed of ninety subjects randomly selected from those recruited during an ongoing epidemiological longitudinal study on adolescent mental health [51]. The study involved subjects living in the urban areas of Lecco, Milan, Rome, Rimini, Pisa, Cagliari and Conegliano Veneto (54 boys and 36 girls; mean age 15.32 ± 2.10 years; age range: 12 to 18 years).

All maltreated and control subjects were Caucasian and of italian descents.

2.2 Procedures

The study protocols were approved by our Scientific Institute Ethical Committee. Legal guardians'or parents' written informed consent was obtained for all participants.

2.2.1 Social questionnaire

The individual and family characteristics of the sample were gathered by the integration of archive data from social services involved in the legal procedure for child maltreatment or abuse and an 'ad hoc' form filled out by legal guardians, thus avoiding further direct leading questions to the children. The form encompassed questions on demographic data (child's gender and age, parents' age, mother's and father's educational level and occupation, numbers of brothers/sisters, family structure: married nuclear, cohabiting, divorced/separated, single-parent, stepfamily), maltreatment (period and type: neglect, physical abuse, emotional abuse and sexual abuse), institutionalization/foster care/adoption (period and length) and contact with social services.

In accordance with the Maltreatment Classification System (MCS) [52] we considered four subtypes of maltreatment. *Neglect* is the failure of a parent or another person who are responsible for the child to provide basic physical needs (food, clothing, shelter and medical care), lack of supervision, moral-legal neglect and educational neglect. *Emotional maltreatment* involves words, actions and indifference; abusers constantly reject, ignore, belittle, dominate and criticize the victims. Examples of emotional child abuse are: verbal abuse; excessive demands on a child's performance; penalizing a child for positive, normal behavior; penalizing a child for demonstrating signs of positive self-esteem; exposing children to family violence and inability to provide affection. *Physical abuse* involves the non-accidental infliction of physical injury on the child (e.g., bruises, choking, broken bones, welts, burns). *Sexual abuse* involves sexual contact between the child and adult for purposes of the adult's sexual satisfaction or financial benefit.

All the maltreated group had documented histories of maltreatment. Among the 52 subjects, 65.4% had experienced neglect, 9.6% had experienced emotional maltreatment, 19.2% had experienced physical abuse and 5.8% had experienced sexual abuse.

In accordance with literature on possible outcomes [20-25], we divided the subjects into two classes of maltreatment: *Physical contact abuse*, which includes physical abuse and sexual abuse (N=13) and *Non-Physical contact abuse*, i.e. neglect and emotional maltreatment (N=39).

2.2.2 Behavioral assessment

The CBCL/6-18 [53] is an empirically based checklist of social competence and behavioral problems filled out by parents of children and adolescents aged 6-18 years. The CBCL/6-18 is divided into two major factors: the internalizing scale (which consists of the anxious-depressed, withdrawn and somatic complaints subscales) and the externalizing scale, which consists of 35 items and two subscales: rule-breaking and aggressive behavior.

In the present study the CBCL/6-18 was filled out by legal guardians. We used parental employment as a measure of socioeconomic status (SES) coded according to the Hollingshead 90-point scale for parental occupation [54]. A score was assigned to each parental job; when both parents were employed, the higher of the two scores was used.

2.2.3 DNA collection and extraction

Genomic DNA was extracted from mouthwash samples collected in 4% sucrose using the DNAzol Genomic DNA Isolation reagent (Molecular Research Center, Cincinnati, OH). We determined the subject's COMT Val158Met genotype using the 5'-exonuclease Taqman assay [55]. Subjects with known genotype, previously typed by sequencing, were used as positive controls. The Taqman primers, probes and reagents were purchased from Applied Biosystems. The assays were performed and analyzed on a 9700HT Sequence Detection System (Applied Biosystems).

2.2.4 Statistical analysis

According to the Val158Met polymorphism, the COMT genotype was classified as Val/Val (N=40), Val/Met (N=75) and Met/Met (N=27). We grouped together Val/Met and Met/Met genotypes (Met-carriers: 71.83%) in opposition to Valcarriers (28.17%) according to literature [46,56]. We preliminarily analyzed the distribution of COMT genotypes across genders, SES classes (low vs. high), presence of maltreatment, and classes of maltreatment by Chi-square analysis. The distributions of the CBCL scores were square-root transformed to attenuate deviations from normality, which led to acceptable kurtosis (min -.207, max .102) and skewness (min .267, max .438) values. The COMT genotype and the Maltreatment Classes (Physical contact abuse vs. Non-Physical contact abuse vs. No-maltreatment) were entered simultaneously as independent variables, while the CBCL/6-18 externalizing behavior was the dependent variable in the univariate-analysis of covariance (ANcOVA), with gender, age and SES as covariates. To better understand to what extent aggressive behavior and rule breaking behavior contributed to our results, we conducted further analysis for these subscales. Statistics were performed using the SPSS 17.0 Software (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL, USA).

3. RESULTS

Socio demographic and behavioral characteristics of the two groups are reported in Table 1.

Table 1. Demographic and behavioral variables (raw data) in the two samples

	Maltreatedchildren	**Control subjects**	***t*-test (*p*)**
Gender (M/F)	30/22	54/36	
Age (years)	15.32 (1.55)	15.32 (2.10)	-.08 (.94)
SES	29.81 (13.50)	54.56 (18.00)	9.28(.000)
Maltreatment			
Neglect	34 (65.4%)		
Emotional Maltreatment	5 (9.6%)		
Physical Abuse	10 (19.2%)		
Sexual Abuse	3 (5.8%)		
Physical contact abuse	13(25.0%)		
Non-Physical contact abuse	39 (75.0%)		
CBCL 6/18			
ExternalizingBehavior	12.12 (9.23)	5.74 (4.51)	-4.55 (.000)
Rule-Breaking Behavior	4.13 (3.80)	1.57 (1.72)	-5.30 (.000)
Aggressive Behavior	7.98 (6.42)	4.18 (3.23)	-3.54 (.001)

We preliminarily analyzed the distribution of COMT genotypes across gender, SES classes, presence of maltreatment and classes of maltreatment by Chi-square analysis and found no significant associations on three level genotypes ($\chi2$=1.35, *df*=2, *p*=.51; $\chi2$=1.30, *df*=2, *p*=.52; $\chi2$=.72, *df*=2, *p*=.70; $\chi2$=1.58, *df*=4, *p*=.83), and on two levels reclassified according to Metcarriers vs. Val-carriers($\chi2$=.79, *df*=1, *p*=.45; $\chi2$=.61, *df*=1, *p*=.55; $\chi2$=.02, *df*=1, *p*=1.00; $\chi2$=.30, *df*=2, *p*=.88).

The genotype frequencies in the total sample were Val/Val 28.17%, Val/Met 52.82%, Met/Met19.01% and the allele frequencies were Val 54.58% and Met 45.42%. The COMT polymorphism was in Hardy-Weinberg equilibrium in the two groups (maltreated subjects: $\chi2$=.96, *df*=1, p=.33; control subjects:$\chi2$=.07, *df*=1, p=.80) and in the total sample ($\chi2$=.61, *df*=1, p=.44).

Table 2 shows the CBCL scores according to COMT genotype and Classes of Maltreatment. Post-hoc analyses of the main effect of Maltreatment classes showed a significant difference between No-maltreatment and Physical and Non-physical contact abuse (p=.04 and p=.01, respectively). Post-hoc analyses of the effect of interaction showed significantly higher Externalizing Behaviors in individuals carrying the Met allele (i.e. Met/Met or Val/Met) who experienced Physical contact abuse than in children of all the other groups (significance range: p =.000–.011) but homozygous for Val-allele with Nonphysical contact abuse (p=.09).

Table 2. Behavioral variables (square-root adjusted) grouped according to COMT genotype and classes of maltreatment

Maltreatment	COMT		Maltreatment	COMT	COMT x Maltreatment
	Met/Met + Val/Met (*n*)	Val/Val (*n*)	*F(p)*	*F(p)*	*F(p)*
ExternalizingBehavior					
None	2.25±.99 (65)	2.05±0.91 (25)			
Non-Physical contact abuse	3.03±1.31 (27)	3.22±1.56 (12)	6.143 (0.003)	4.995 (0.03)	3.320 (0.04)
Physical contact abuse	3.97±1.30 (10)	1.96±1.10 (3)			
Rule -Breaking Behavior					
None	.97±.79 (65)	1.00±0.79 (25)			
Non-Physical contact abuse	1.77±.93 (27)	1.84±1.02 (12)	4.707 (0.01)	5.099 (0.03)	3.895 (0.02)
Physical contact abuse	2.13±.98 (10)	0.47±0.82 (3)			
Aggressive Behavior					
None	1.94±.85 (65)	1.66±0.81 (25)			
Non-Physical contact abuse	2.35±1.18 (27)	2.54±1.40 (12)	5.299 (0.006)	3.801 (0.053)	2.523 (0.08)
Physical contact abuse	3.30±1.06 (10)	1.85±0.92 (3)			

The univariate-analysis of covariance (ANcOVA), with gender, age and SES as covariates, revealed a significant effect of COMT (p=.03) of Maltreatment Classes (p=.003) and of COMT x Maltreatment Classes (p=.04; Fig. 1.) on Externalizing Behavior.

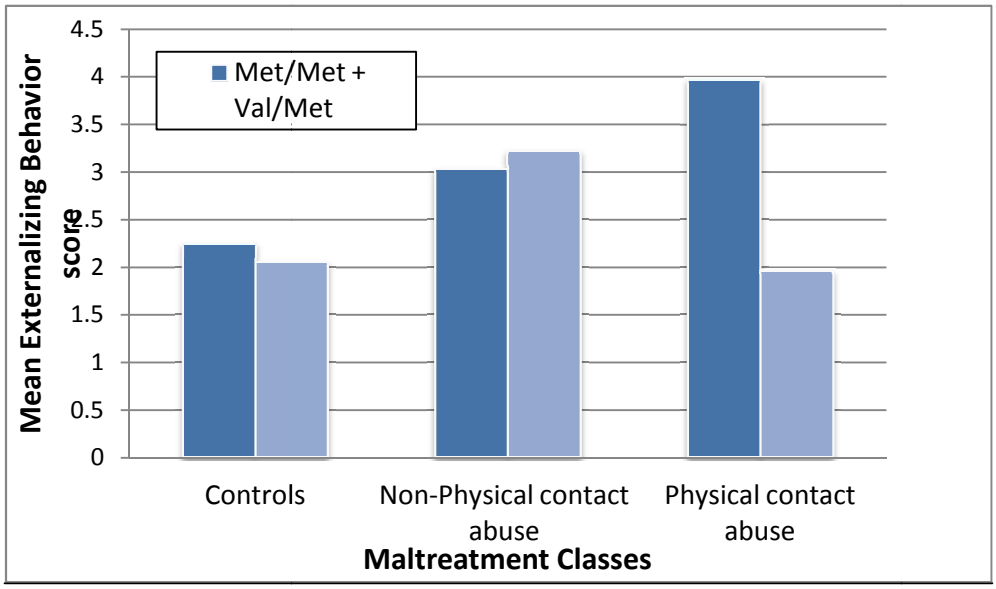

Fig. 1. CBCL 6/18 Externalizing Behavior (square-root adjusted) according to Maltreatment' Classes x COMT genotype

When we repeated the analysis with Rule-Breaking Behavior as dependent variable we found the same results: COMT, Maltreatment Classes and COMT x Maltreatment Classes had a significant effect on this scale (p=.03, p=.01 and p=.02, respectively). Post-hoc analyses on main effect showed a significant difference only between No-maltreatment and Non-physical contact abuse (p=.03); post-hoc analyses on interaction showed that Met-carriers with Physical contact abuse differed significantly from Met-carriers with No-altreatment (p=.002) from homozygous for the Val-allele with No-maltreatment (p=.004) or with Physical contact abuse (p=.005).

Finally, when we analyzed Aggressive Behavior as dependent variable, Maltreatment Classes (*p*=.006) had a significant effect while we found only a trend for COMT (*p*=.053) and for COMT x Maltreatment Classes (*p*=.08). Post-hoc analyses on main effect showed that No-maltreatment was significantly different from Physical- and Non-physical contact abuse (*p*=.02; *p*=.06). Met-carriers who experienced Physical contact abuse had higher scores compared to all other subject (significance range: *p*=.000–.04), with the exception of children homozygous for Val-allele and with Non-physical contact abuse (*p*=.053).

3. DISCUSSION

This is a preliminary study on the effects of child maltreatment in a population sample of children and adolescents aged 13-18, with a control-group. It is the first study that has investigated the association of the COMT Val158Met polymorphism and child maltreatment with a range of behavioral problems in a gene-environment perspective (G x E) dividing this risk factor into two major categories based on the presence or absence of physical contact.

Our main findings show that COMT Val158Met polymorphism interacts with childhood Physical contact abuse to influence externalizing behavior as assessed using the CBCL/6-18 [53]. In the presence of Physical contact abuse, individuals carrying the Met allele (i.e.

Met/Met or Val/Met) display higher externalizing symptoms than individuals without history of maltreatment or respect to all subjects' homozygotes for the Val allele. This result was also found for Aggressive Behavior scale but not for Rule Braking Behavior Scale.

Interestingly, we found higher externalizing behavior in maltreated children (independently of the type of maltreatment). These data are in agreement with many studies in literature suggesting a positive association between externalizing behavior and maltreatment [10-12,23]. Herein, we have reported a possible contribution to the understanding of the association between externalizing behavior and maltreatment showing that the effects of different classes of maltreatment' upon behavioral phenotypes could possibly be moderated by genetic risk factors. Previous studies in literature found positive associations between externalizing behavior and COMT genotype: Albaught et al. [46], reported a strong association between youths carrying a Met allele and higher average Aggressive Behavior scores on the CBCL/6-18 relative to Val-homozygotes, after controlling for demographics, SES, and maternal parenting quality as confounders. Similarly, in our study we found a possible association of COMT Val158Met polymorphism and externalizing and rule-breaking problems, while for aggressive problems the association was non-significant. These findings are also consistent with Bilder's tonic-phasic dopamine hypothesis about relationship between COMT and behavior [40]. This model postulates increased levels of dopamine in the prefrontal cortex of Met-carriers that leads to the excessive rigidity typical of externalizing behavior. Moreover, recent functional neuroimaging studies suggest that the Met allele is positively associated with neural activity in prefrontal and amigdala regions during the processing of negative emotional stimuli [57-59] and that this brain region influenced by the Met allele overlaps with areas involved in externalizing behaviors like aggression [60]. As regards the contribution of putative risk variables in individual differences, our findings suggest that the COMT Val158Met genetic susceptibility to externalizing phenotypes could moderate the effect of child maltreatment, in its different forms. Although the preliminary nature of this study needs further investigations and replications, our starting hypothesis would seem to be confirmed in that the interaction between genetic and environmental factors explains children behavioral response to maltreatment. Our data underline the fact that the type of maltreatment is very likely to be a key-factor in studies of gene-environment interaction in the context of child maltreatment; inconsistency of results reported in literature could be related to the lack of consideration of this feature of maltreatment in previous research. The way in which physical maltreatment got "under the skin" of the child could be the result of different biological mechanisms relating to non-physical maltreatment.

Since this is a preliminary study, our results should be regarded with some limitations.

Firstly, the sample size was quite small, especially considering the high frequency in the general population of the polymorphism analysed. Considering also the high frequency of behavioural consequences in abused children as well, these results should be considered as very preliminary and would need to be extended through further recruitment of subjects to improve the statistical power of results.

Secondly, the use of only one measure to assess externalizing behavior makes it impossible to perform sensitivity analysis, i.e., to see whether G x E effects hold across different phenotypic measures that map the same diagnostic construct in the attempt to reveal spurious G x E due to scaling effects [28,29].

Thirdly, the use for maltreated subjects of legal-guardian-rated CBCL questionnaires only, while for the control subjects questionnaires were filled out by parents. It is reasonable to

assume that the assessment of the externalizing behavior made by these two sources of information raises the possibility of informants-bias because they have a different depth of knowledge of children. Nevertheless, we used this procedure because some data in literature suggest that the CBCL/6-18 is a reliable and valid measure for use by guardians to assess behavior problems [61]. A direct assessment through direct interviews would remain by definition the most informative and reliable method.

These preliminary results need to be confirmed through further research that exceeds the above limits. In addition, an interesting hypothesis would be to further clarify the role of gene and environment, for example through sib-pair study.

4. CONCLUSION

This is the first study investigating the association between externalizing behavior and physical contact vs. non-physical contact forms of child maltreatment as well as the moderating role of the COMT Val158Met polymorphism on this association in an adolescent population. Our finding that Physical contact abuse could possibly be associated with externalizing problems in COMT Met/Met and Val/Met carriers illustrate the importance of studying gene-environment interactions in attempting to improve our understanding of the behavioral correlates of COMT and of child maltreatment.

CONSENT

All authors declare that ‘written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee, Scientific Institute, IRCCS Eugenio Medea and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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