

CONTENTS

Infection Due to Adenovirus 36 and Childhood Obesity
The Best of ESPID 2012

EDITORIAL BOARD

Co-Editors: Delane Shingadia and Irja Lutsar

Board Members

| | | |
|--|--|---|
| <i>David Burgner (Melbourne, Australia)</i> | <i>Nicole Ritz (Basel, Switzerland)</i> | <i>Tobias Tenenbaum (Mannheim, Germany)</i> |
| <i>Luisa Galli (Florence, Italy)</i> | <i>Ira Shah (Mumbai, India)</i> | <i>Marc Tebruegge (Southampton, UK)</i> |
| <i>Cristiana Nascimento-Carvalho (Bahia, Brazil)</i> | <i>Matthew Snape (Oxford, UK)</i> | <i>Marceline van Furth (Amsterdam, The Netherlands)</i> |
| <i>Ville Peltola (Turku, Finland)</i> | <i>George Syrogiannopoulos (Larissa, Greece)</i> | <i>Anne Vergison (Brussels, Belgium)</i> |



Is There a Link Between Infection Due to Adenovirus 36 and Childhood Obesity?

Susanna Esposito, MD, Valentina Preti, MD, Erica Nazzari, MD, Silvia Consolo, MD, and Nicola Principi, MD

Childhood obesity has more than tripled over the last 30 years. About 17% of Americans aged 2–19 years are obese¹ as are 8% of Europe’s school-age children.² Most obese children remain obese during adulthood, and this can lead to hypertension, dyslipidemia, type 2 diabetes, coronary heart disease, stroke, sleep apnea, respiratory problems, osteoarthritis, some types of cancer and psychological problems.^{1,2}

Obesity is a chronic disease of multiple etiologies, but the most important factors leading to fat accumulation in children are genetic inheritance, endocrine alterations, and behavioral/environmental causes such as diet, lack of exercise, cultural practices and stress.³

Evidence emerging over the last 20 years supports the hypothesis that viral infections may be associated with obesity in animals and humans, and this review

considers the data indicating a link between viral infection and childhood obesity.

VIRAL INFECTIONS AND OBESITY IN EXPERIMENTAL ANIMALS

The first report of obesity associated with a viral infection was published in 1982 and, since then, a number of studies have investigated the possibly causal relationship between infections and obesity.^{4–13} Five infectious agents have so far been implicated: canine distemper virus, rous-associated virus 7, scrapie, borna disease virus and adenoviruses.^{4–13} Apart from adenoviruses, all the other viruses of this list are associated with brain damage and, in experimental animals, the obesity develops via brain involvement or via direct damage of fat tissue.

Canine distemper virus is a paramyxovirus that infects dogs and other wild mammals, and an association between canine distemper virus infection and obesity has been found in mice.⁴ It has been suggested that a necessary condition for the development of obesity is viral replication in mouse brain (particularly the hypothalamus) with decreased levels of catecholamine, leptin receptors and the substances involved in energy regulation and food intake.⁴

Rous-associated virus 7 is one of the most common retroviruses affecting chickens, in which it may cause obesity involving the central nervous system and is associated with hypertriglyceridemia and hypercholesterolemia regardless of food intake.⁵ Another possible mechanism related to rous-associated virus 7–induced obesity

involves alterations in the thyroid with lymphoblastoid infiltration, decreased levels of thyroid hormones and hypothyroidism.⁶

Scrapie is caused by infectious prion proteins, which may cause a neurodegenerative disease in sheep with a long incubation period. Once again, obesity is considered to be a consequence of central nervous system lesions. It has been shown that removing the adrenal gland in mice may protect against obesity.⁷ Diabetes is also associated with scrapie and is not only due to obesity but also due to pancreatic damage.⁷

Borna disease virus is a nonsegmented negative-stranded RNA virus that may cause obesity in various animals, including rats and chickens. Most studies suggest that borna disease virus causes obesity by damaging the hypothalamus with accumulating viral particles.⁸

Finally, adenoviruses are very common and may cause a variety of infections in birds and mammals, including humans. Four strains of adenoviruses have been associated with animal obesity: SMAM-1 and adenoviruses 36, 37 and 5. SMAM-1 has been associated with increased body fat in chickens.^{9–13} Chickens with peritoneal SMAM-1 infection have 50% more abdominal fat than control chickens and decreased serum triglyceride and cholesterol levels apparently due to liver damage.⁹

Adenovirus 36 has a close affinity for fatty tissue, and its DNA has been found in quantities correlating with body fat in mice and chickens.¹⁰ The brains of mice infected with adenovirus 36 have been evaluated in an attempt to find an alteration

From the Pediatric Clinic 1, Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Milan, Italy.

This review was supported by a grant from the Italian Ministry of Health (Bando Giovani Ricercatori 2009). The authors have no other funding or conflicts of interest to disclose.

Address for correspondence: Susanna Esposito, MD, Pediatric Clinic 1, Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Via Commenda 9, 20122 Milan, Italy. E-mail: susanna.esposito@unimi.it.

Copyright © 2012 by Lippincott Williams & Wilkins
ISSN: 0891-3668/12/3111-1184
DOI: 10.1097/INF.0b013e31826f114f

The ESPID Reports and Reviews of *Pediatric Infectious Diseases* series topics, authors and contents are chosen and approved independently by the Editorial Board of ESPID.

that could cause lesion, but no lesions were found.¹⁰ Experiments inoculating monkeys with adenovirus 36 have shown an association with weight gain, increased visceral fat and decreased serum lipid levels.¹¹ It is thought that the most important mechanism of action of adenovirus 36 is a direct effect on adipose tissue through the upregulation of *C/EBP β* , one of the genes that play a critical role in preadipocyte differentiation. It has also been demonstrated that adenovirus 36 can be transmitted horizontally from one infected chicken to another sharing the same cage, and that the transfusion of a small amount of blood from adenovirus 36-infected animals successfully transmits infection and obesity to the recipients.¹²

Adenoviruses 37 and 5 have respectively been associated with increased visceral fat in chickens and mice during the 3–5 weeks after infection even without any difference in food intake.¹³ In the case of these 2 adenoviruses, oxidative stress is considered a possible cause of obesity as the fat cells of obese animals produce increased levels of toxic oxygen molecules and the enzyme nicotinamide adenine dinucleotide phosphate. All of these findings raise the question as to whether at least some cases of childhood obesity can be considered as being due to an infectious disease.

VIRAL INFECTIONS AND OBESITY IN CHILDREN

There are relatively few published studies of virus-induced obesity in humans, particularly during childhood. Human subjects cannot be experimentally infected for ethical reasons and so it is difficult to obtain direct proof that viruses can increase body fat. The most widely studied virus as a possible cause of childhood obesity is adenovirus 36. No clear data are available on the other viruses mentioned earlier and their association with human obesity.

Na et al selected 318 Korean school-children (255 obese and 59 nonobese) aged 6–15 years and observed a closer relationship between a positive adenovirus 36 antibody status and lipid disorders in the obese group than in the nonobese group (28.6% versus 13.6%; $P = 0.0174$) in absence of specific symptoms.¹⁴ The obese participants who were adenovirus 36 antibody-positive had higher triglyceride and total cholesterol levels than those who were adenovirus 36 antibody negative.¹⁴ After adjusting for age, gender and obesity, the risk of high triglyceride levels was twice as great in the antibody-positive than in the antibody-negative subjects, which suggests that previous adenovirus 36 infection may be an independent risk factor for high triglyceride levels.¹⁴ This finding contradicts those of earlier

adult studies showing that adenovirus 36 antibody-positive obese and nonobese subjects paradoxically had lower triglyceride and total cholesterol levels than those who were adenovirus 36 antibody negative.¹⁵

In 2010, Atkinson et al¹⁶ determined the prevalence of adenovirus 36 infection in 84 obese Korean children and found that 25 (30%) had antibodies against adenovirus 36. The infected children had significantly higher body mass index Z scores (1.92 versus 1.65; $P < 0.01$) and larger waist circumferences (96.3 versus 90.7 cm; $P = 0.05$) than the uninfected ones.

The most recent study of a pediatric population was performed by Gabbert et al,¹⁷ who studied a total of 124 children, 46% non-obese and 54% obese. Nineteen children (15% of the population) were positive for adenovirus 36-specific neutralizing antibodies, and 15 of these (78%) were obese. Furthermore, adenovirus 36 positivity was significantly more frequent in the obese children (22% versus 7%).¹⁷ Among the children who were obese, those who were adenovirus 36 positive had significantly larger anthropometric measures (including body mass index, weight, waist circumference and waist/height ratio).¹⁷

In 2011, Atkinson wrote a review about the relationship between adenovirus 36 infection and obesity in childhood based on findings in a total of 559 children enrolled in 3 published studies or described in an oral presentation. Overall, these studies showed that there is an increase in prevalence of adenovirus 36 infection in obese children (28% versus 10%).¹⁸

The pediatric data concerning viral infections and obesity are in line with the findings of animal studies. On the contrary, some adult studies seem to indicate a strict relationship between seroconversion against adenovirus 36 and increased weight and altered lipid metabolism, whereas others lead to partially or totally different conclusions.¹⁸ Various factors may explain some of the differences among the human studies and between them and the animal or in vitro studies. It is not easy to evaluate adenovirus 36 antibodies and, although highly specific and sensitive, the method is labor intensive and lengthy. Moreover, it has been found that immune responses can be significantly impaired in obese people and that the reduction in antibody concentrations is proportional to the severity of obesity.

However, the results of the various human studies may also have been greatly influenced by the fact that obesity is a multifactorial disease and, in most cases, fat accumulation is caused by a number of concomitant factors. Experimental studies are always prospective, and selected animals or cells are infected with adenovirus 36; however, human studies are always

retrospective, and the presence of previous adenovirus 36 infection is established by measuring adenovirus 36 antibodies without taking into account the time the infection occurred, viral load or the duration of the persistence of the virus in the body. Consequently, various confounding factors can be eliminated a priori in prospective studies, and it is easier to make a more precise evaluation of the effects of adenovirus 36 infection, whereas it is frequently impossible to remove or identify the coexisting causes of obesity in retrospective studies and, therefore, significantly more difficult to analyze the results.

The age of the infected host can also be important when studying the role of adenovirus 36. Some of the causes of childhood obesity (particularly those related to behavior) are less common and/or important in adults, at least in some countries, and this means that the effect of adenovirus 36 infection may be more easily demonstrated in the first years of life. This may also explain why the relationship between adenovirus 36 infection and obesity is apparently stronger in pediatric studies than in adult studies.

CONCLUSION

Adenovirus 36 is the main virus that studies of experimental animals and humans have shown to be associated with the development of obesity. The childhood findings are also interesting but more research is needed to identify the pathogenic mechanism and consequences of the infection. The prevalence of adenovirus 36 infection in the general population as well as what happens to adenoviral antibodies over time remain unknown. However, as obesity is a multifactorial disease, it is very difficult to identify in which obese children infection is the only cause of obesity. As not all subjects infected by adenovirus 36 develop obesity, it would be interesting to know why some are protected, and an analysis of which genetic factors play a role in this regard may help to identify those at higher risk. However, if the preliminary data are confirmed, new studies will be necessary to evaluate potential antiviral therapies capable of inhibiting disease progression and possible vaccines.

REFERENCES

- Ogden CL, Carroll MD, Curtin LR, et al. Prevalence of high body mass index in US children and adolescents, 2007–2008. *JAMA*. 2010;303:242–249.
- Wang Y, Lobstein T. Worldwide trends in childhood overweight and obesity. *Int J Pediatr Obes*. 2006;1:11–25.
- McAllister EJ, Dhurandhar NV, Keith SW, et al. Ten putative contributors to the obesity epidemic. *Crit Rev Food Sci Nutr*. 2009;49:868–913.
- Griffond B, Verlaeten O, Belin MF, et al. Specific alteration of the expression of selected hypothalamic

- neuropeptides during acute and late mouse brain infection using a morbillivirus: relevance to the late-onset obesity? *Brain Res.* 2004;1022:173–181.
5. Carter JK, Garlich JD, Donaldson WE, et al. Influence of diet on a retrovirus-induced obesity and stunting syndrome. *Avian Dis.* 1983;27:317–322.
 6. Bode L, Ludwig H. Borna disease virus infection, a human mental-health risk. *Clin Microbiol Rev.* 2003;16:534–545.
 7. Kim YS, Carp RI, Callahan SM, et al. Adrenal involvement in scrapie-induced obesity. *Proc Soc Exp Biol Med.* 1988;189:21–27.
 8. Herden C, Herzog S, Richt JA, et al. Distribution of Borna disease virus in the brain of rats infected with an obesity-inducing virus strain. *Brain Pathol.* 2000;10:39–48.
 9. Dhurandhar NV, Kulkarni PR, Ajinkya SM, et al. Association of adenovirus infection with human obesity. *Obes Res.* 1997;5:464–469.
 10. Dhurandhar NV, Israel BA, Kolesar JM, et al. Increased adiposity in animals due to a human virus. *Int J Obes Relat Metab Disord.* 2000;24:989–996.
 11. Dhurandhar NV, Whigham LD, Abbot DH, et al. Human adenovirus Ad-36 promotes weight gain in male rhesus and marmoset monkeys. *J Nutr.* 2002;132:3155–3160.
 12. Dhurandhar NV, Israel BA, Kolesar JM, et al. Transmissibility of adenovirus-induced adiposity in a chicken model. *Int J Obes Relat Metab Disord.* 2001;25:990–996.
 13. Atkinson RL. Viruses as an etiology of obesity. *Mayo Clin Proc.* 2007;82:1192–1198.
 14. Na HN, Hong YM, Kim J, et al. Association between human adenovirus-36 and lipid disorders in Korean schoolchildren. *Int J Obes (Lond).* 2010;34:89–93.
 15. Goossens VJ, deJager SA, Grauls GE, et al. Lack of evidence for the role of human adenovirus-36 in obesity in a European cohort. *Obesity (Silver Spring).* 2011;19:220–221.
 16. Atkinson RL, Lee I, Shin HJ, et al. Human adenovirus-36 antibody status is associated with obesity in children. *Int J Pediatr Obes.* 2010;5:157–160.
 17. Gabbert C, Donohue M, Arnold J, et al. Adenovirus 36 and obesity in children and adolescents. *Pediatrics.* 2010;126:721–726.
 18. Atkinson RL. Human adenovirus-36 and childhood obesity. *Int J Pediatr Obes.* 2011;6 (suppl 1):2–6.