

'Hyperemesis hiemis': new light on an old syndrome

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SRSVs are a significant cause of gastroenteritis which have only been identified in recent years. Now molecular methods are aiding the research into the transmission and diagnosis of these organisms.

● Diarrhoeal illness in man is second only to respiratory disease in terms of morbidity and mortality. Despite original reports of a gastrointestinal illness termed 'hyperemesis hiemis' or 'winter vomiting disease' in 1929 by an American physician, it was not until almost 45 years later that a causative agent was identified for this syndrome. A further 25 years was to elapse before the full scale of the prevalence of the role of this agent in gastrointestinal infection was recognized.

This diarrhoeal disease was originally established in the USA as non-bacterial in origin with widespread outbreaks occurring primarily in families during the winter season. Numerous descriptive terms were subsequently coined by various workers, including 'non-bacterial gastroenteritis', 'epidemic vomiting disease' and 'acute infectious gastroenteritis'. A viral aetiology was suspected by the use of oral administration of faecal filtrates to human volunteers which reproduced the disease, fulfilling Koch's postulates. However, all attempts to isolate the viral agent in conventional cell and organ cultures failed. Despite comprehensive epidemiological studies allied to transmission of the agent to human volunteers, a specific aetiology (cause) for this gastrointestinal infection could not be established. This failure over many years hampered progress in identifying the agent causing worldwide epidemics.

● Identification of the infectious agent

However, in 1972, following an outbreak of gastroenteritis in a primary school in the USA, a small round 32 nm virus with a clearly resolved amorphous surface structure lacking geometric symmetry was eventually identified by electron microscopy. It was named Norwalk virus after the town in Ohio where the outbreak took place. Soon after, the widespread application of electron microscopy led to the identification of a variety of other morphologically distinct small round viruses in stools. Some of these had no distinguishing structure visible in the electron microscope and were shown not to be associated with disease. Other small round viruses associated with gastroenteritis were identified and specifically named according to their definitive surface structure, including the astrovirus (five/six-pointed star) and the classic caliciviruses (cup-shaped indentations on the surface of the virus giving the appearance of the Star of David). Other viruses indistinguishable from Norwalk virus by electron microscopy were identified in stool samples from gastroenteritis outbreaks around the world and, as in the case of Norwalk virus, were named after the location of the outbreak, e.g. Hawaii, Montgomery County, Toronto, Bristol, Southampton and Desert Shield (Gulf War), to name but a few.

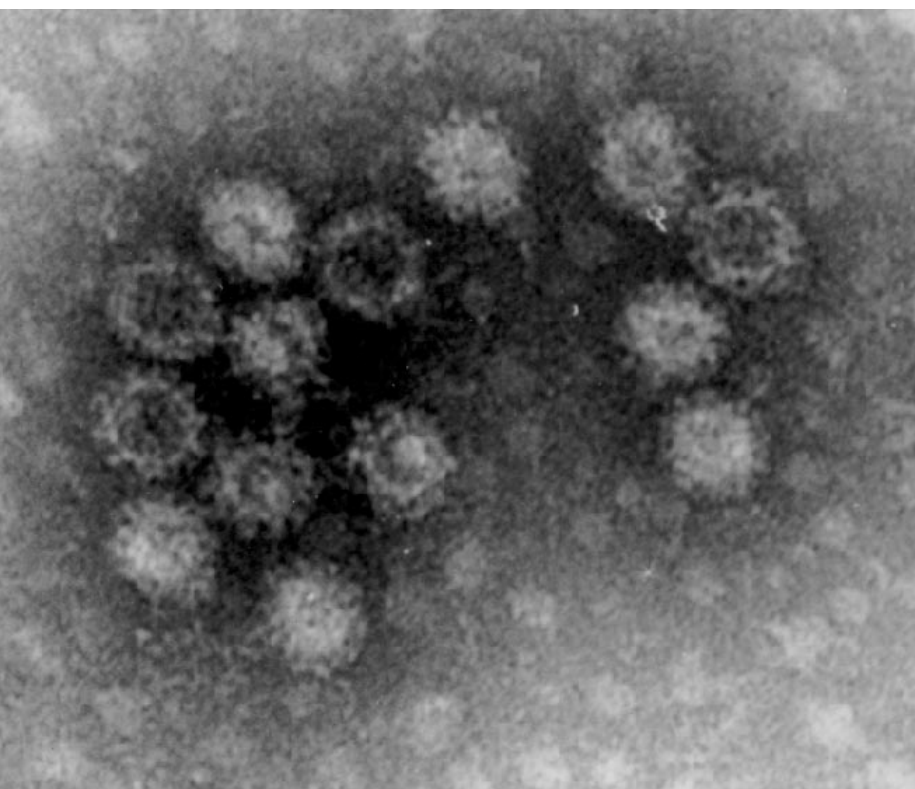
● Classification of small round structured viruses (SRSVs)

Some order was brought to the recognition of the small round viruses with the introduction of a classification scheme in 1982. This led to the use of the term small round structured viruses (SRSVs) to describe viruses structurally indistinguishable in the electron microscope from the original Norwalk virus, but clearly distinct from astroviruses and the 'classical' caliciviruses. In the UK, this scheme established the role of all the small round viruses as aetiological agents in non-bacterial gastroenteritis. As a result the SRSVs became identified as the most important cause of epidemic gastroenteritis in the UK and worldwide. The virus is known to affect all age groups in contrast to astroviruses and caliciviruses which are often the causal agents in sporadic cases of paediatric diarrhoea and uncommonly as causes of outbreaks.

● Genome sequencing

Complete genome sequences are available for three human SRSVs: the prototype Norwalk virus and two from the UK, Southampton and Lordsdale viruses. Genome sequencing studies have revealed that SRSV genomes consist of approximately 7.5–7.7 kb single-stranded RNA, polyadenylated at the 3' terminus. The genomes have three open reading frames (ORFs), including a large ORF encoding the non-structural proteins preceding a second ORF encoding a viral capsid

BELOW:
Electron micrograph showing typical appearance of SRSVs. The virus particles are approximately 30 nm in diameter.
PHOTO: C. ASHLEY, PHLS





vomiting (often projectile) is a common presenting feature of the illness, an additional mode of transmission became plausible because of the large numbers of virus particles present in vomit (>20 million ml⁻¹) and the aerosols generated in acute infection. The nature of sudden-onset diarrhoea and projectile vomiting means that environmental contamination occurs and

LEFT:
Aerosol spread by projectile vomiting!
COURTESY WILLIAM H.J. BUTTON

protein and a short 3'-terminal ORF that encodes a small basic protein of unknown function. SRSVs can be divided into two genogroups based upon comparisons of nucleotide sequences from various parts of the viral genome. All of these features have led to the classification of the SRSVs within the *Caliciviridae*. However, on the basis of genome organization and sequence analyses, enteric caliciviruses with the classic morphology have been assigned to a separate genus within the *Caliciviridae*. The SRSVs remain clearly distinct from the classic human caliciviruses not only in terms of genomic characteristics and morphology but also in their epidemiology and immunobiology.

SRSVs have also been recognized by direct electron microscopy of faecal specimens from animal species. However, it was not until recently that the complete genome sequence for a bovine enteric calicivirus (Jena virus) was obtained. This clearly showed that this animal virus was closely related to the human viruses. Phylogenetic studies with Jena virus showed that it belongs to genogroup 1 (the same genogroup as the prototypical Norwalk virus). In contrast, a recent partial sequence analysis of cDNA obtained from the caecum contents of pigs detected the presence of viruses belonging to genogroup 2.

The recent characterization of SRSVs isolated from animal faeces demonstrates that these viruses are very similar to their human counterparts and raises intriguing questions about their zoonotic potential. It is likely that with improved methods of detection these enteric caliciviruses will be found widely distributed throughout the animal kingdom.

● Transmission of SRSVs

SRSVs cause acute, explosive diarrhoea and/or vomiting and are highly infectious, with rapid secondary spread. Human volunteer studies established that the virus was spread through the faecal-oral route but this mode of transmission alone could not explain the explosive outbreaks documented. Subsequently, SRSVs were identified in vomit from affected patients. As

this has been demonstrated recently. The infective dose is very low (10–100 particles) making transmission via aerosolized vomit a reality. Anecdotal support is provided by outbreaks where groups of people gathered together in enclosed spaces, e.g. on a bus, in a restaurant, on cruise ships and at wedding receptions, are ill following a vomiting incident, despite being distant from the event. Consequently, outbreaks have the potential to spread rapidly, and so semi-closed communities such as hospital wards, old people's homes, cruise ships and holiday centres are common sites of outbreaks. The consequences of outbreaks in health care have both financial and managerial implications. Ward closure often results from staff shortages due to illness and widespread infection.

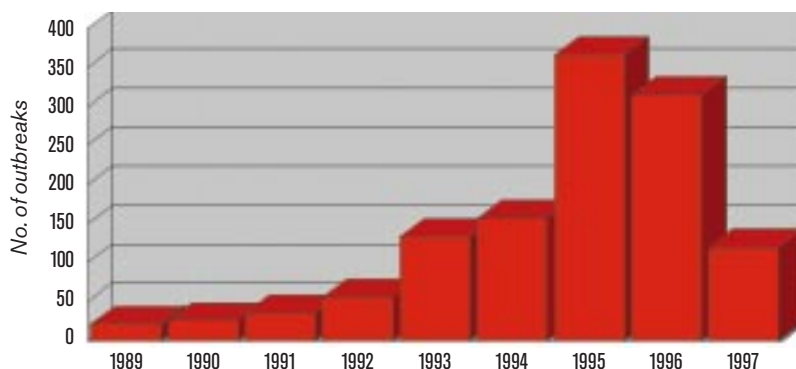
● SRSVs in food

Another dimension of the impact of SRSVs is in the food industry. Point source outbreaks have been reported as a result of sewage-contaminated water used for bathing, drinking or preparation of food. Salads, sandwiches and other cold foods being prepared and contaminated by ill food handlers have been widely reported. Oysters, which are usually eaten uncooked, serve as a reservoir to concentrate SRSVs from contaminated estuaries or seawater where they grow. As a result the virus is delivered appropriately to the intestine of the unsuspecting diners. Consequently, amorous diners in search of the aphrodisiac properties of oysters on Valentine's Day are often left with a most unexpected moving experience some 24–48 hours later. With the increase in the scale of food production and ever-expanding distribution networks, the potential for large national and international outbreaks is inevitable.

● Diagnosis – new methods

Although the role of SRSVs in gastroenteritis outbreaks is now well recognized, the scale of their involvement in the population has only recently been acknowledged in the UK. Routine diagnosis primarily relies on

SRSV positive outbreaks in England and Wales between 1989 and 1997



Data for 1996 and 1997 are provisional. Courtesy CDSC, CPHL Colindale

Further reading

Caul, E. O. (1996). Viral gastroenteritis: small round structured viruses, caliciviruses and astroviruses. Part I. The clinical and diagnostic perspective. *J Clin Patbol* 49, 874–880.

Caul, E. O. (1996). Viral gastroenteritis: small round structured viruses, caliciviruses and astroviruses. Part II. The epidemiological perspective. *J Clin Patbol* 49, 959–964.

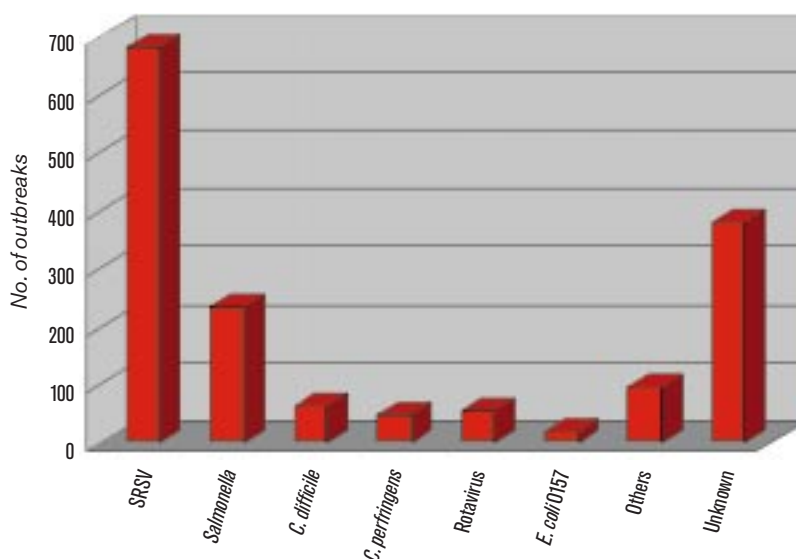
Clarke, I. N. & Lambden, P. R. (1997). The molecular biology of caliciviruses. *J Gen Virol* 78, 291–301.

Clarke, I. N., Lambden, P. R. & Caul, E. O. (1998). Human enteric RNA viruses: caliciviruses and astroviruses. In *Topley & Wilson's Microbiology and Microbial Infections*, pp. 511–535. Edited by B. W. J. Mahy & L. Collier. London: Arnold.

Liu, B. L., Lambden, P. R., Günther, H., Otto, P., Elschner, M. & Clarke, I. N. (1999). Molecular characterization of a bovine enteric calicivirus: relationship to the Norwalk-like viruses. *J Virol* 73, 819–825.

electron microscopy since, in spite of intensive laboratory efforts, the virus cannot be cultured. Electron microscopy is relatively insensitive and is dependent on good timely sampling from acutely ill patients. More recently the advent of molecular techniques has allowed characterization of complete and partial genomes of several SRSVs. Methodologies based upon the polymerase chain reaction (PCR) have been applied to outbreak diagnosis. Although PCR has proved more sensitive than electron microscopy, the need to apply extensive 'clean-up' on patient specimens to obtain viral RNA of sufficient purity for analysis hampers its widespread use. Molecular assays are more technically demanding and are only suitable for relatively small numbers of samples and therefore cannot be applied in most laboratories. However, molecular epidemiology has revealed that the SRSVs can be divided into two broadly diverse genetic groups and that the diversity of strains has allowed characterization of large foodborne SRSV outbreaks affecting large geographical areas. The real benefit of molecular techniques, however, has only recently been realised. Cloned SRSV capsid genes can be expressed in cell culture systems leading to the formation of virus-like particles (VLPs) which are morphologically and antigenically representative of the real virus. In the absence of conventional virus culture these recombinant VLPs have allowed the generation of strain-specific immunological reagents which can be applied to simple diagnostic tests and sero-epidemiological surveys. Such epidemiological studies have been applied in many countries and reveal that most children have been exposed to SRSVs by 5 years of age. Although the disease symptoms can be distressing to the individual, they are relatively mild and clear quickly, and so probably go unreported in most cases. However, volunteer studies showed that immunity is strain-specific and short-lived, but the widespread occurrence of the disease in conjunction with the antigenic diversity of SRSVs and

General outbreaks of infectious intestinal disease in England and Wales, 1995–1996



Data from Evans et al. (1998) *Commun Dis Public Health* 1, 165–171

the low infectious dose means that numerous episodes of exposure and illness should be expected in the lifetime of an individual.

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