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Genetic sperm defects

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Abstract

Genetic sperm defects are specific sperm defects, which have been shown to have a genetic mode of transmission. Such genetic linkage, either direct or indirect, has been associated with a number of sperm defects in different species, with this number increasing with improved diagnostic capabilities.

A number of sperm defects, which have proven or suspected genetic modes of transmission are discussed herein, with particular emphasis on cattle. These include:

1. Acrosome defects (knobbed, ruffled and incomplete);
2. Head defects (abnormal condensation, decapitated, round head, rolled head, nuclear crest);
3. Midpiece abnormalities (''Dag'' defect, ''corkscrew'' defect, ''pseudo-droplet'' defect);
4. Tail defects (''tail stump'' defect, primary ciliary dyskinesia).

Keywords: Genetic sperm defects; Male fertility; Sperm morphology

1. Introduction

Sperm abnormalities have long been associated with male infertility and sterility in most species studied. These abnormalities vary from morphological defects that are evident upon clinical examination, to those, which are more subtly defective. In general, sperm structure can play a substantial role in both fertilization and pregnancy outcome [1–7]. The causes of defective sperm structure may be environmental, genetic, or a combination of both. Although environmental causes are considered to be most common, there is a growing list of sperm structural defects, which are considered to be of genetic origin.

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Even though the heritability of bull fertility is generally considered to be low, certain aspects of bull fertility, including sperm morphological abnormalities, are under genetic control [5]. Earlier work [8] associated sire differences with the proportion of normal sperm, including a tendency for inbred bulls to have more morphological sperm abnormalities than line-cross bulls. This was reinforced by further work with the same lines of bulls [9], in which degree of inbreeding was associated with increased proportions of abnormal seminiferous tubules. Much of the variation (62%) in non-return rate using frozen semen was associated with bulls [2], although this study included only AI bulls previously screened for genital health and semen quality (which would tend to reduce the adverse effects of those variables).

2. Definitions

A number of classification systems exist for sperm abnormalities, including the following.

2.1. Primary and secondary sperm defects

Sperm abnormalities have been classified on the basis of their presumptive origin [10,11]. In this system, defects which occur during spermatogenesis are considered as primary and those developing subsequent to spermiation considered as secondary. Although primary defects were originally considered to be caused by some type of direct insult to the seminiferous epithelium, they were not automatically assumed to be more deleterious to fertility than secondary defects, which could be induced by a variety of causes, including iatrogenic. Later interpretations of this system included assumptions that primary defects are more adverse to male fertility than secondary defects [12], and that the latter are more variable and less consequential than the former. These assumptions are undergoing serious review in light of recent developments in cell biology and proteomics.

2.2. Major and minor sperm defects

The primary/secondary classification was revised [13] as exceptions to the rule became evident. In the revised system, sperm defects were classified as either major or minor in terms of their perceived adverse effects upon male fertility. Here, major sperm defects were those, which had proven to be associated with impaired fertility, and minor sperm defects were those which were generally considered to be of minor consequence to male fertility. Further definition of major sperm defects (sometimes referred to as specific sperm defects) included the following criteria:

1. They are well characterized ‘‘primary’’ sperm defects,
2. They occur in a substantial proportion (at least 10–15%) of the sperm population,
3. They are consistent in occurrence,
4. They are associated with male infertility or sterility,
5. They may be heritable.

Table 1
Major and minor sperm defects in the bull [13]

Major	Minor
Underdeveloped	Narrow heads
Double forms	Small normal heads
Acrosome defect (knobbed acrosome)	Giant and short broad heads
Decapitated sperm defect (active tails)	Free normal heads
Diadem defect	Detached acrosome membranes
Pear-shaped defect	Abaxial implantation
Narrow at base	Distal droplet
Abnormal contour	Simple bent tail
Small abnormal heads	Terminally coiled tail
Free pathological heads	Other abnormal cells
Corkscrew defect	Epithelial cells
Other midpiece defects (tail stump)	Erythrocytes
Proximal droplet	Medusa formation
Pseudodroplet	Boat cells
Strongly coiled or folded tail (‘‘Dag’’ defect)	Round cells
	Pus cells

A further tacit caveat is that such defects occur in the absence of a clinically or environmentally discernable cause.

This system was used to develop a presumptive list of major and minor sperm defects in the bull [13] (Table 1).

Considerable overlap occurs between this system (based upon known effects upon fertility) and the primary/secondary system (based upon origin of the defect), to the extent that lists of sperm defect categories in either system are strikingly similar. Closer scrutiny however suggests that a number of ‘‘minor’’ defects most probably occur prior to spermiation (e.g. subtle sperm head abnormalities and abaxial implantation). Certainly, effective use of the major/minor sperm defect system also requires critical interpretation. For example, as knowledge grows in areas of cell biology, genomics and proteomics, our understanding of sperm ‘‘fertility’’ becomes more complicated and the list of ‘‘major’’ sperm defects tends to increase. In addition, computer-assisted image analysis enables us to identify subtle shape differences between sperm [14]. We now better understand that the spermatogenic epithelium responds to a wide variety of stressors in a predictable fashion, such that many sperm abnormalities previously regarded as being finite entities are now considered to be different representations of the same response process. This stereotyped spermatogenic stress response is characterized, at one end of the spectrum, by the subtle diadem defect of sperm, which cascades through to gross sperm head abnormalities with increasing severity or duration of spermatogenic stress (Fig. 1).

2.3. *Compensable and uncompensable semen traits*

Abnormal sperm may reduce fertility in one of two ways: (1) failure to reach the fertilization site; or (2) inability to fertilize the ovum once they are at the fertilization site or to sustain development of the early embryo [15]. In the first case, failure of sperm to reach the fertilization site can often be traced to problems in sperm transport. Sperm defects

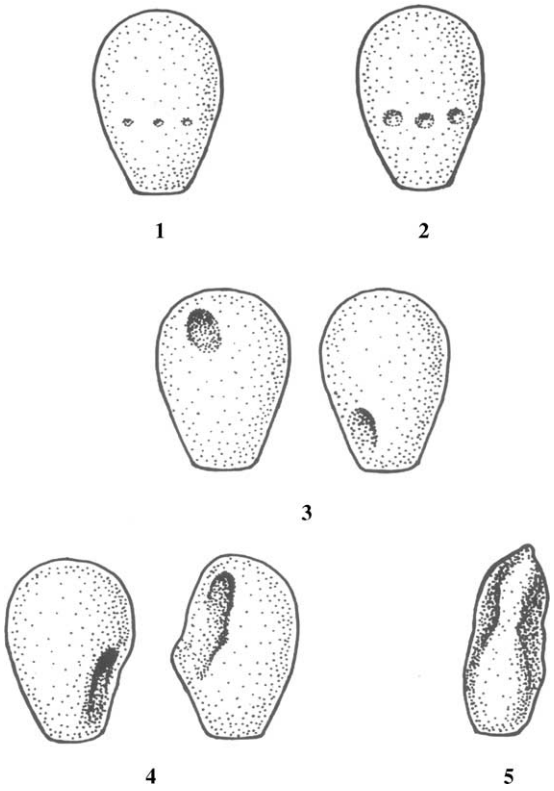

Fig. 1. The crater/diadem defect and its sequelae.

which cause either impaired sperm motility, or reduced probability of successfully transcending the female tract, are termed compensable defects. This is because a theoretical increase in numbers of functionally competent sperm will solve, or mitigate, the problem. Those defects which lead to failed fertilization or early pregnancy loss are termed uncompensable [15]. With these defects, an increase in sperm numbers alone will theoretically not improve fertility.

2.4. Genetic sperm defects

Under natural breeding conditions, there is continuous natural selection against inherited factors, which reduce fertility. In addition, natural barriers occur within the male and female tract to remove faulty gametes. However, modern breeding methods, particularly those involving advanced assisted reproductive technologies (e.g. IVF, ICSI), may circumvent these principles and barriers such that genetic infertility factors may be propagated via subfertile males [16]. In this discussion, we will focus upon genetic sperm defects where the following quotation is relevant. ‘‘Some types of defects appear in the semen at a fairly constant rate and in a very high proportion of the sperm cells without any

indication of environmental influence. Such defects may be presumed to be rooted in the bull's genome and the prognosis for future improvements in semen quality would be very poor'' [12].

Genetic sperm defects are those that have been shown to have a genetic mode of transmission. Such genetic linkage has been associated with a number of sperm defects in different species, with this number increasing with improved diagnostic capabilities. However, it should be noted that other sperm defects, more variable in nature that may be influenced by an interaction of environment and genetic predisposition. The elucidation of the genetic basis of sperm defects presents difficulties and it is no coincidence that the number of identified genetic sperm defects is related to the rate of adoption of AI of the species involved. Thus, the number of genetic sperm defects identified in cattle is considerably greater than in many other species. This should not, however, imply that cattle are more afflicted in this regard than are other species. Rather, they have probably undergone more scrutiny than most. Such scrutiny should follow appropriate protocols, such as those described below, to properly establish a genetic basis for the defect in question. Here, the National Association of Artificial Breeders (NAAB) in USA recognizes the importance of identifying genetic faults, as is evident by the following quotation. ''The major responsibility of NAAB is to assure that effective programs are implemented by the AI industry... to control the proliferation of economically important gene defects''. To firmly establish a nominate defect as having a genetic basis, the NAAB requires the following questions to be answered:

1. Has evidence been provided that establishes the presence of the condition in the cattle population?
2. Is the mutation within germinal or somatic cells?
3. What breed (or breeds) is involved?
4. Is the condition lethal, and at what time in life is the condition expressed?
5. What proportion of the population may be affected?
6. Are similar conditions known in other species?
7. Is there evidence of a selective advantage for a heterozygote?
8. Are tests currently available to detect the condition?
9. Are the tests definitive and what are their limitations?

Once the problem is recognized as an adverse genetic condition, it is important to establish the following:

1. Its physiological basis.
2. Its mode of inheritance.
3. Its economic consequences.
4. An accurate rapid and inexpensive diagnostic test.
5. Control procedures.

Interestingly, in its deliberations to date, the NAAB has not identified any genetic sperm defects. Rather, the current approved lists of identified genetic defects in both dairy and beef cattle contain structural, neurological and biochemical defects only. In the following

discussion, attempts are made to identify, in animals of veterinary interest, a number of relevant sperm defects, which are either known or suspected to have a genetic basis, at least on occasion.

3. Categorization of genetic sperm defects

3.1. Acrosome

3.1.1. Knobbed acrosome defect

This sperm defect was first reported in a sterile Friesian bull [17] and subsequently associated with an autosomal sex-linked recessive mode of genetic transmission in this breed [18]. It has been associated with infertility in bulls, boars and rams [16,19,20]. In boars, the defect has been associated with both dominant [21] and sex-linked recessive [22] modes of transmission. There is some evidence that it exists as a genetic defect within the Angus breed in North America (Chenoweth unpublished) and there is a suggestion of a genetic linkage in Charolais cattle [12].

In the bull, the major manifestations of this abnormality are: (1) a refractile, thickened acrosomal apex; and (2) an indented sperm apex [23]. Electron microscopy often reveals a cystic region (‘‘cystic apical body’’ [24]) containing vesicles with inclusions, as well as abnormal fusion of acrosomal membranes [24,25]. There is also often a bending back, or abrupt termination, of sperm nuclear material [23].

Elevated levels of knobbed acrosomes (KA) in bull semen may be caused by either environmental or genetic factors. When environmental, they are usually transitory and associated with other signs of spermatogenic dysfunction (i.e. increased sperm abnormalities in general, including nuclear vacuoles). A genetic cause is suspected when high proportions of sperm exhibit the KA defect in the absence of frequent numbers of other sperm abnormalities, and when the defect persists at a consistently high level [23]. In Canada, 78 of 1331 (0.53%) bulls had sperm with knobbed acrosomes (cause unknown) [12]. In contrast, in our laboratory, we found an estimated genetic prevalence of 6.74% in a known affected Angus herd (unpublished). Sperm containing KA either lack the ability to attach to ova [26] or have reduced capability to do so [23]. If this were the only adverse effect of KA, then this defect would satisfy the ‘‘compensable’’ category, whereby increasing sperm numbers could compensate for damaged sperm. In fact, this may help explain an observed difference between natural and AI fertility of a KA affected ram [20]. In addition, the proportion of KA sperm was shown to decrease during transit in the cow’s genital tract [27]. Despite these findings, in vitro studies indicate that apparently normal sperm from animals affected by KA may also have compromised fertility [20]. Further studies have shown that these apparently morphologically normal sperm can have plasma membrane damage, and show premature capacitation, spontaneous acrosome reaction, and impaired chromatin condensation [28]. Thus the KA defect may encompass both ‘‘compensable’’ and ‘‘uncompensable’’ characteristics. As bulls with apparently similar proportions of the defect may vary in infertility, this variation may be either due to such unrecognized causes of sperm dysfunction, or to the numbers of undamaged sperm reaching the fertilization site.

3.1.2. Ruffled and incomplete acrosomes

Ruffled and incomplete acrosomes have been reported in subfertile bulls where they were linked with the knobbed acrosome defect [16]. Here, ruffled acrosomes had an irregular staining pattern leading to a wrinkled, or ruffled, appearance. Incomplete acrosomes had an irregular margin; giving the appearance that part of the acrosome was missing or incomplete. A genetic basis was suggested by the occurrence of the three defects (knobbed, ruffled and incomplete acrosomes) in four sons of a subfertile Holstein sire. Some similarity has also been drawn with acrosome abnormalities described in ''genetically-determined quasi-sterile'' male mice [29].

3.2. Sperm head defects

3.2.1. Abnormal DNA condensation

''Differences in spermatozoan DNA exist, not only among individuals of the same species but also among sperm in the same ejaculate'' [30]; a reference related to Fuelgen-DNA staining patterns of sperm. Abnormal sperm DNA condensation (''clumping'') is difficult to identify using routine sperm morphology techniques. However, the use of flow cytometry, in concert with DNA-specific fluorochromes, was effective in detecting the degree of heterogeneity of sperm nuclear chromatin structure; this was associated with disturbances of spermatogenesis, sperm abnormalities and infertility in a number of species [31]. It is included in this discussion as it may provide an example of genetic-environmental interactions on sperm structure. A Canadian Simmental bull identified with this condition showed variable levels of infertility as well as DNA ''clumping'', with the latter appearing to increase over the summer months [12].

3.2.2. Decapitated (disintegrated) sperm defect

Separation of the sperm head and tail can be caused by a number of adverse factors affecting either spermiogenesis or sperm maturation [12]. However, a specific, sterilizing form has been reported in several cattle breeds (Guernsey, Hereford, Swedish Red & White) where it has been associated with sterility. Most (80–100%) of sperm are affected, with the separated tail usually remaining motile. In addition, the proximal end of the separated midpiece is often curled around a cytoplasmic droplet, giving the appearance perhaps of a micro-cephalic sperm head. The separation has been associated with defective development of the sperm head, implantation grove and basal plate, and becomes evident when sperm are traversing the epididymis [32,33]. Evidence for the hereditary nature of this defect in bulls (most probably via a sex-limited recessive gene with male and female carriers) has come from several reports [34–36]. A similar defect was reported in a group ($n = 8$) of Hereford bulls [37], in which testicular hypoplasia ($n = 5$) was also diagnosed.

The following characteristics have been proposed as being indicative of this specific sperm abnormality [38]:

1. Sperm heads and tails are separated in 80–100% of ejaculated sperm,
2. A high percentage of the loose tails show active movement,
3. A proximal bending or curling of the middle-piece around the cytoplasmic droplet is often seen.

3.2.3. Round-headed sperm

This defect has been reported in four infertile men (two of whom were brothers), where it affected 100% of ejaculated sperm [39]. Many of the sperm heads contained vacuole-like structures, while none had an acrosome attached.

3.2.4. Rolled-head, nuclear crest, giant head syndrome

A combination of abnormalities (rolled-head, nuclear crest and giant heads) have been observed to occur in combination in some bulls. Where such abnormalities occur in substantial numbers, there have been suggestions of hereditary linkages [12]. The ultrastructure of sperm with rolled heads and nuclear crests has been described [40]. It is suggested that rolled sperm represent a deviated form of the giant sperm head abnormality [12,41], and that they are often diploid (and occasionally triploid or even tetraploid) [12,42]. Bulls with this defect generally exhibit a consistent spermiogram over time [12]. Both the nuclear crest and rolled head defects were also reported to be caused by ethylene-dibromide spermatoxicity [43]. Although effects of this sperm defect upon fertility are unclear [12], it is logical to assume that abnormal chromosome numbers in sperm would compromise fertility, as encountered in males with Kleinfelter's syndrome [44].

3.3. Sperm midpiece defects

3.3.1. "Dag" defect

Named after the Jersey bull in which the defect was first identified, this defect is represented by strong folding, coiling and fracture of the distal part of the sperm midpiece (with or without a retained distal cytoplasmic droplet). A consistent similar spermiogram was observed in a full brother to ''Dag'', suggesting a hereditary basis. However, an environmental link with dietary zinc has also been suggested [45]. The defect may reflect disturbance in the testis or epididymis and may be present ($<4\%$) in normal semen. Levels above 50% can have serious fertility implications [12]. A similar defect has been reported in a subfertile boar [46], although a genetic basis was not established.

3.3.2. "Pseudo-droplet" defect

This was first reported in five Friesian bulls in Denmark [47] where the defect was encountered in 7–26% of ejaculated sperm. As the affected bulls were all related (two were half-brothers), a hereditary basis was suggested. The semen samples from the affected bulls were usually of normal concentration, although initial sperm motility was poor. The percentage of affected sperm tended to increase with bull age.

The defect was characterized by a local thickening on the midpiece. Although they could resemble cytoplasmic droplets under normal microscopy, they are prone to occur in regions where droplets are seldom encountered (e.g. the middle of the midpiece). They are also more likely to be irregular in shape and more visually dense than droplets. Ultramicroscopically, they comprised accumulations of granules surrounded by mitochondria.

A ''mictotubular mass defect'' of spermatozoa was reported in the semen of seven Standardbred stallions, in which a genetic link was suggested [48]. Here, irregular masses in the proximal region of the midpiece contained torturous arrays of small abnormal

microtubules. Similar structural defects (termed ''knobs'') were observed in a sterile stallion [49], where they represented mitochondrial accumulations.

Similar irregular midpiece formations in bull semen have been associated with Bovine Ephemeral Fever [50] and also with gossypol spermatoxicity [51]. In the latter case, these masses were also caused by abnormal accumulations and clumping of mitochondria.

3.3.3. ''Corkscrew midpiece'' defect

The ''corkscrew sperm defect'' was first described in ejaculated sperm of two sterile bulls [52] where it was observed as an irregular distribution (''lumps'') of mitochondria, resembling a corkscrew under light microscopy. A genetic cause was suggested as four of the first five detected bulls were related. However, similar defects have been reported in bulls following Bovine Ephemeral Fever [50], in a sterile stallion [49] and in bulls undergoing gossypol spermatoxicity [52]. Further doubt concerning the genetic basis of this defect came from the original source, who associated an observed temporal increase of this defect in Danish bulls with concurrent increased levels of radioactive fallout [53]. Here, an environmental-genetic interaction may have been evident as the Red Danish breed appeared to be particularly susceptible to the spermatoxic effect in question.

3.4. Sperm tail defects

3.4.1. Coiled tails

Simple coiled tails (a term now understood to include the distal midpiece reflex) are among the most common sperm defects. Often, an increased prevalence of such defects in the ejaculate is associated with a one or more of a variety of non-genetic origin etiologies.

3.4.2. ''Tail stump'' defect

This defect was first reported in bulls in 1925 [1]. It has also been encountered in the mouse, rabbit, dog, stallion and man [12]. Three sterile Canadian bulls (Ayrshire, Shorthorn, Holstein) showed virtual absence of the sperm midpiece and tail in the majority of ejaculated sperm, where they were represented by a small ''stump'' or ''stub'' [54]. In addition, sperm concentration was very low and sperm motility was virtually absent. Monitoring of sperm morphology in these bulls indicated that the percentage of sperm with the defect increased with the age of the bulls. It has been suggested that a prevalence of greater than 25% of this defect in the ejaculate is suggestive of a genetic fertility problem [12]. Other reports have linked this defect with sterility in bulls [55–57], and suggestion has been made of an inherited mode of transmission [12,58,59]. It has also been linked with infertility in boars [60] and reported in man as well as mice. Care should be taken to differentiate this condition from the ''accessory tail defect'' in bulls, which probably shares a common etiology with abaxial sperm midpieces, as well as little impact upon fertility [61].

3.4.3. Primary ciliary dyskinesia (previously termed immotile cilia syndrome)

This is represented by a diverse group of disorders characterized by a structural and generalized abnormality of ciliated cells. In man, a systemic axonemal alteration is associated with Kartagener's syndrome in which the males are infertile and possess

immotile spermatozoa [62]. Here, in common with other ciliated cells in the body (such as respiratory epithelial cells) affected sperm (and respiratory tract cilia) have perturbed axonmenal structures, e.g. part or complete absence of dynein arms, microtubule disorganization, or absent radial spokes [63]. This suggests a genetic link between these structures or that they are coded by the same gene. Similar sperm aberrations exist in the animal world, although the link with respiratory diseases has not been adequately pursued. It should be noted that the axonemal complex contains over 200 proteins, defects in any of which could be related to problems with genetic coding. Similar alterations to sperm tail axonemal complexes have been identified in genetically similar mice, which were sterile [62].

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