PART III

Guest Lecture  ON THE PATHOGENESIS OF SEXUAL DYSFUNCTION OF THE URAEMIC MALE

Chairman: A Válek
ON THE PATHOGENESIS OF SEXUAL DYSFUNCTION OF THE URAEMIC MALE

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Both the female and male patients with advanced uraemia complain of abnormalities in sexual function. These include a decline in the interest in sex, reduced libido, decreased frequency of intercourse, and impaired ability to achieve orgasm. Most of the available studies, however, deal with the issue of impotence in the male patient and our discussion will also relate to the impotence of the uraemic subjects and those treated with dialysis.

Evaluation of the incidence of impotence among uraemic patients was done either by psychiatric interviews with the patients and/or their spouses or by sending questionnaires to the patients. The results of these studies are summarised in Table I. They revealed that 1) reduced or partial impotence is present in 38–80% of dialysis patients while total impotence was reported by 20–55% of the patients, and 2) frequency of intercourse is decreased with the development of uraemia, and further decline may occur during maintenance haemodialysis [1–7].

It is generally accepted that psychological disturbances are major causes underlying the sexual dysfunction and particularly the impotence in these patients. However, this assumption was made without critical evaluation of the affective state of the patients and without correlating the incidence or severity of impotence with depression, anxiety or other psychological disturbances. In addition, the above mentioned studies ignored possible organic causes of impotence, did not consider the effect of ageing on potency [8, 9] and did not evaluate whether the state of chronic illness or uraemia per se is the critical factor. Finally, one must approach these data with caution since the information submitted by the patients on their sexual profile might not be as reliable and accurate as one would like.

The pathogenesis of impotence in the uraemic patient is complex and may include both psychological disturbances as well as organic abnormalities. Some of the possible factors that may contribute to the impotence are listed in Table II. It is apparent, therefore, that a meaningful approach to the elucidation of the incidence and pathogenesis of the impotence in uraemia should satisfy at least two conditions. First, such a research should utilise an objective criteria for the
TABLE I. Summary of the reported data on impotence and frequency of intercourse in patients treated with dialysis

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients number</th>
<th>Reduced potency</th>
<th>Total number</th>
<th>Impotence complete</th>
<th>Impotence partial</th>
<th>Frequency of intercourse per week before uraemia</th>
<th>Frequency of intercourse per week during dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>n %</td>
<td>n %</td>
<td>n %</td>
<td>0 &lt; 1 &gt; 1</td>
<td>0 &lt; 1 &gt; 1</td>
</tr>
<tr>
<td>Friedman et al 1970 [2]</td>
<td>6</td>
<td>5</td>
<td>83</td>
<td>18</td>
<td>10</td>
<td>8 38</td>
<td></td>
</tr>
<tr>
<td>Abram et al 1975 [6] *</td>
<td>32</td>
<td>25</td>
<td>78</td>
<td>12</td>
<td>12</td>
<td>10.4</td>
<td>5.7 4.0</td>
</tr>
<tr>
<td>Thurm 1975 [7] *</td>
<td>22</td>
<td>12</td>
<td>55</td>
<td></td>
<td></td>
<td>8–12</td>
<td>&lt; 4</td>
</tr>
</tbody>
</table>

* Interview
+ Questionnaire
TABLE II. Possible causes of decreased sexual potency in uraemia

1. Psychological factors
2. Chronic illness
3. Hormonal factors  
   a) Abnormalities in hormones of the hypothalamic-pituitary-gonadal axis: FSH, LH, Testosterone and prolactin  
   b) Hyperparathyroidism
4. Autonomic neuropathy
5. Disturbances of trace metal metabolism: zinc deficiency
6. Medications for hypertension

Evaluation of the disturbances of potency in addition to the information submitted by the patients; and, second, the investigation should be comprehensive, should examine various possible organic disturbances, and should carefully evaluate the affective and psychological state of the patient.

Measurement of the magnitude and duration of the penile erectile activity during rapid eye movement sleep at night may provide an objective approach for the evaluation of potency [10]. The nocturnal penile tumescence (NPT) could be recorded throughout the night using two mercury strain gauges attached to the tip and base of the penis and electronic recorder. We have evaluated NPT in 48 uraemic patients including 23 treated with maintenance dialysis, 22 patients with chronic illness and normal renal function, and in 50 normal subjects [11]. Psychiatric interviews were also performed to obtain information on the affective state of the patients and on their sexual profile. About 40–50% of uraemic patients but not those with chronic illness and normal renal function complained of erectile dysfunction and reported a significant decrease in frequency of intercourse. There was no significant difference between the uraemic patients prior to initiation of dialysis therapy and those treated with maintenance haemodialysis. NPT declined after 40 years of age. In all groups, NPT was significantly lower in uraemics than in normal subjects or those with chronic illness. There was no correlation between erectile complaints, frequency of intercourse or NPT and the presence or absence of depression. The frequency of intercourse correlated significantly with NPT in uraemic patients. The data indicate 50% of male uraemic patients have partial or complete impotence which is most probably organic in nature and is related to uraemia or its metabolic or hormonal consequences rather than to the state of chronic illness.

Disturbances in sex hormones are known to occur in patients with uraemia. The abnormalities in the hypothalamic-pituitary-gonadal axis have been evaluated in 133 patients reported in 10 publications [12–21]. These data (Table III) revealed that 1) the blood levels of testosterone are almost always low but they may increase following administration of human chorionic gonadotrophin (HCG) or clomiphene, 2) the blood levels of luteinising hormone (LH) are elevated in about 50% of the patients, 3) the blood levels of follicle-stimulating hormone (FSH) are usually normal but may be elevated, and 4) prolactin levels in blood are elevated in many male dialysis patients with or without gynaecomastia. We
<table>
<thead>
<tr>
<th>Author</th>
<th>Type of patient</th>
<th>Patients number</th>
<th>Blood levels</th>
<th>Testosterone after HCG</th>
<th>Testosterone after C</th>
<th>LH</th>
<th>FSH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guevara et al 1969 [12]</td>
<td>CRF (8) PD (4) HD (14)</td>
<td>26</td>
<td>↓</td>
<td>N</td>
<td>↑14/26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chen et al 1970 [13]</td>
<td>CRF (3) PD (7) HD (5)</td>
<td>15</td>
<td>↓</td>
<td>N</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bailey et al 1970 [14]</td>
<td>before HD after HD</td>
<td>5</td>
<td>↓ increased</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Sawin et al 1973 [17]</td>
<td>HD gynaecomastia</td>
<td>5</td>
<td>N</td>
<td>↑4/5</td>
<td>↑1/5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stewart-Bently et al 1974 [18]</td>
<td>HD</td>
<td>7</td>
<td>↓</td>
<td>N</td>
<td>↑delayed</td>
<td>variable</td>
<td>variable</td>
</tr>
<tr>
<td>Distiller et al 1975 [19]</td>
<td>HD (8) PD (8)</td>
<td>16</td>
<td>↓7/16</td>
<td>↑4/16</td>
<td>↑8/16</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FSH = follicle-stimulating hormone; LH = luteinising hormone; HCG = human chorionic gonadotrophin; HD = haemodialysis; CRF = chronic renal failure; PD = peritoneal dialysis; C = clomiphene
have also found in our uraemic patients similar disturbances in the blood levels of testosterone, FSH, LH and prolactin.

Similar abnormalities in the blood levels of the hormones of the hypothalamic-pituitary-gonadal axis become quickly apparent even in patients with acute renal failure. We have studied 20 such patients and found that blood levels of FSH and testosterone are significantly reduced and those of prolactin are significantly elevated throughout the entire course of the oliguric phase of the illness. Recovery of renal function was associated with normalisation of the hormonal disturbances [22].

A cause and effect relationship between these hormonal aberrations and impotence is not established since in almost all of the endocrine studies no attempt was made to correlate the disturbances in sex hormones with impotence. Hagen et al [21] attempted such a correlation. They found that 11 of their 21 dialysis patients were impotent but there was no discernable relationship between the blood levels of the various hormones and sexual potency. In fact, the blood levels of prolactin were elevated in 6 of the 11 impotent patients and in 6 of the 10 patients with normal potency. It must be emphasised that the presence or absence of impotence in their studies was based on information submitted by the patients. On the other hand, preliminary results from our laboratory demonstrate a significant and direct correlation between NPT and blood testosterone levels. In addition 10 of 15 patients with elevated prolactin or LH had reduced NPT while 9 of 13 patients with normal prolactin or LH had normal NPT. These observations point toward an important role for the aberrations in sex hormones in the genesis of the disturbances in NPT and hence impotence in uraemia.

Several lines of evidence suggest that the state of secondary hyperparathyroidism in uraemia may be partly involved in the aetiology of sexual dysfunction. We have noticed that two dialysis patients who were impotent for several years were able to exercise adequate sexual activity after parathyroidectomy. Loew et al [23] studied sexual function in 33 dialysis patients and found that 24 of these had various degrees of impotence. They found a significant correlation between the degree of impotence and the magnitude of secondary hyperparathyroidism. We also noticed that the majority of some 40 dogs which were subjected to parathyroidectomy and bilateral nephrectomy developed permanent erection which lasted until their demise. Furthermore, suppression of parathyroid gland activity with 1,25(OH)\textsubscript{2}D\textsubscript{3} was associated with normalisation of the blood levels of sex hormones and improved potency [24]. It appears that excess parathyroid hormone (PTH) in the blood of uraemic patients may participate in the pathogenesis of impotence and provide another organic basis for the sexual dysfunction of renal failure. Further studies are needed to elucidate this possibility.

The possible pathways through which PTH may affect sexual function are listed in Table IV. We have previously demonstrated the deleterious effects of PTH on the central and peripheral nervous system [25–28]. Also, PTH is known to enhance entry of calcium in various tissues. A change in the calcium content of the hypothalamus, pituitary or testes may affect their secretory function. Indeed, Bundschuh et al [29] found calcium deposits in the testicular tubules of dialysis patients. Preliminary data from our laboratory demonstrated that three days of acute uraemia in dogs is associated with a significant increase in calcium
TABLE IV. Possible mechanisms through which PTH may affect sexual potency

1. Disturbances in central nervous system
2. Disturbances in peripheral nervous system
3. Alterations in cellular content of calcium in hypothalamus, pituitary or testes and, as such, affecting hormonal synthesis and/or secretion
4. Stimulation of prolactin production

content of hypothalamus, anterior pituitary and testis and with a significant fall in blood levels of testosterone. These abnormalities in acutely uraemic dogs could be prevented by prior parathyroidectomy and could be reproduced in dogs with normal renal function by the administration of PTH. Finally, Isaac et al [30] found that the administration of PTH or the stimulation of endogenous PTH in normal subjects produced an immediate rise in the blood levels of prolactin. We also found that a significant correlation between the blood levels of prolactin and those of PTH in patients with acute renal failure [22].

Antoniou et al [31] reported that zinc deficiency may be a cause of impotence in uraemia. They added zinc to the dialysate used in the management of four impotent patients. This procedure produced a marked elevation in their zinc blood levels over a period of several months. The hyperzincaemia was associated with improvement in sexual potency as ascertained by the patients’ claim. In addition Mahajan et al [32] found that zinc supplementation in 10 dialysis patients was associated with normalisation in blood levels of testosterone, a fall in the blood levels of LH and a significant increase in sperm counts. They further found that plasma zinc was directly correlated with plasma testosterone and inversely with plasma LH. Confirmation of these data and correlation between normalisation of the blood levels of sex hormone and improvement in potency with zinc supplementation would add another organic pathway in the apparently very complex processes responsible for the impotence of uraemia.

Finally, preliminary data from our laboratory demonstrated a relationship between NPT and the disturbances in the autonomic nervous system induced by uraemia, an observation emphasising the organic nature of the impotence commonly seen in the patients with advanced renal failure.

In summary, the mechanisms underlying the pathogenesis of impotence in uraemia are not, as yet, elucidated. It has been suggested that psychological factors play a paramount role in the causation of impotence in patients with renal failure. However, review of the available evidence and results of studies carried out by us and by others indicate that organic disturbances such as abnormalities in hormones of the hypothalamic-pituitary-gonadal axis, the state of secondary hyperparathyroidism, disturbances in zinc metabolism and autonomic nervous system dysfunction are more critical factors.

Acknowledgments

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References

5. Salvatierra O, Fortmann JL, Belzer FO. Urology 1975; 5:64
7. Thurm J. Urology 1975; 5:60
20. Lim VS, Fang VS. Amer J Med 1975; 58:655
27. Goldstein DA, Massry SG. Miner Electrolyte Metab 1978; 1:84

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