APPLIED PERSPIRATION TEST IN *Diabetic Autonomic Neuropathy*

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This paper was presented in Asean Federation of Endocrine Societies VI, Jakarta, July 2 - 4, 1992

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Applied perspiration test in diabetic autonomic neuropathy

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Abstract

Autonomic neuropathy is a frequent complication of diabetes mellitus. Disorders of sweating due to degeneration of post ganglionic sudomotor axons are common expression of diabetic autonomic neuropathy. Perspiration test is one of the simple methods for measuring sweat gland activity. Sweating was evaluated by diaphoretic procedure or heat sweating was produced by the use of external heat.

The result of 30 patients suspected of having neuropathy on the basic clinical examination, had unequinovocal abnormalities on the perspiration test. Pathologic loss of sweating occurred distally in 37%, segmentally in 20%, focal sweat loss in 20%, global anhidrosis in 6%, and normal pattern in 17% of the patients.

Introduction

Diabetic neuropathy commonly involves a variety of nerves, including autonomic fibers and produces several distinct clinical syndromes(*10*). Disorders of sweating due to degeneration of post ganglionic sudomotor axons are common expression of Diabetic Autonomic Neuropathy (**DAN**).(*12*)

From an anatomic viewpoint the autonomic nervous system was divided into thoracolumbar (sympathetic) and craniosacral (parasympathetic) divisions.(*1*)

By Rundles in 1945, the characteristic symptom complexes of **DAN** for first clearly delineated.(*3,17*) And pioneering studies by Wiliamson, Jordan and Rundles then systematically confirmed that neurological findings are complication of diabetes mellitus.(*11*) Although **DAN** is now well recognized as serious consequence of diabetes mellitus most of the clinical features were described 40 years ago, the

pathofisiological understanding is still far from complete.(*8*)

AN is frequent complication of diabetes mellitus often accompanies or even precedes the first signs of the more commonly recognized sensory motor polyneuropathy.(*12*) About 50% the symptoms are asymptomatic rising with altered test of autonomic function are considered. (*7*) With simple methods of perspiration test, dysfunction of sympathetic by measuring sweat gland activity can be observed.

Diabetic Autonomic Neuropathy

Definition: Diabetic Autonomic Neuropathy is generalized dysfunction of the autonomic nervous system, of uncertain etiology and insidious onset, unpredictably and unevenly affecting the various areas of the body. (*9*)

The prevalence of **DAN** is uncertain to know, there have been no adequate studies of prevalence of symptoms in **DAN**, although varying percentages have been found in selected series. In several previous studies, were found about 17 - 40 % of diabetic subjects have abnormal cardiovascular autonomic function tests according to most large series. According to Ari Sutjahjo et all in study Diabetic Autonomic Neuropathy and impotency was found a prevalence of 50 % of diabetic subjects. (*15,16*) According to Macleod A.F was found a prevalence of 7,5 % on discovery of diabetes, increasing to about 50 % after 25 years (*14*). So this prevalence of **AN** increases with the duration of disease and with poor control of blood glucose. (*14,16,17*). According to Canal N and Pozza G (*4*) about 40 % of autonomic failure it occurs in case of diabetes of more than 10 years, parasympathetic damage occurs earlier and is more severe than sympathetic modification. The relationship between duration of diabetes and abnormalities.

duration of diabetes:

≤ 1 year : 0 % (S) and 5,2 % (P.S)
1 - 5 years: 7,8 % (S) and 18,4 % (P.S)
6 - 10 years: 22,5 % (S) and 29,0 % (P.S)
> 10 years: 22,2 % (S) and 35,1 % (P.S)

Vagal impairment sometimes occurred without any sympathetic involvement but not the reserve. Sympathetic defects were also common, but generally less severe and more difficult to assess. (*13*) Autonomic symptoms are uncommon in young diabetic subjects, although there have been occasional case reports of severe symptomatic autonomic neuropathy. (*8*). According to Chandra B, all patients were older than 40 years and occurred frequently during fifth and sixth decades of life. (*2*)

Abnormal morphology

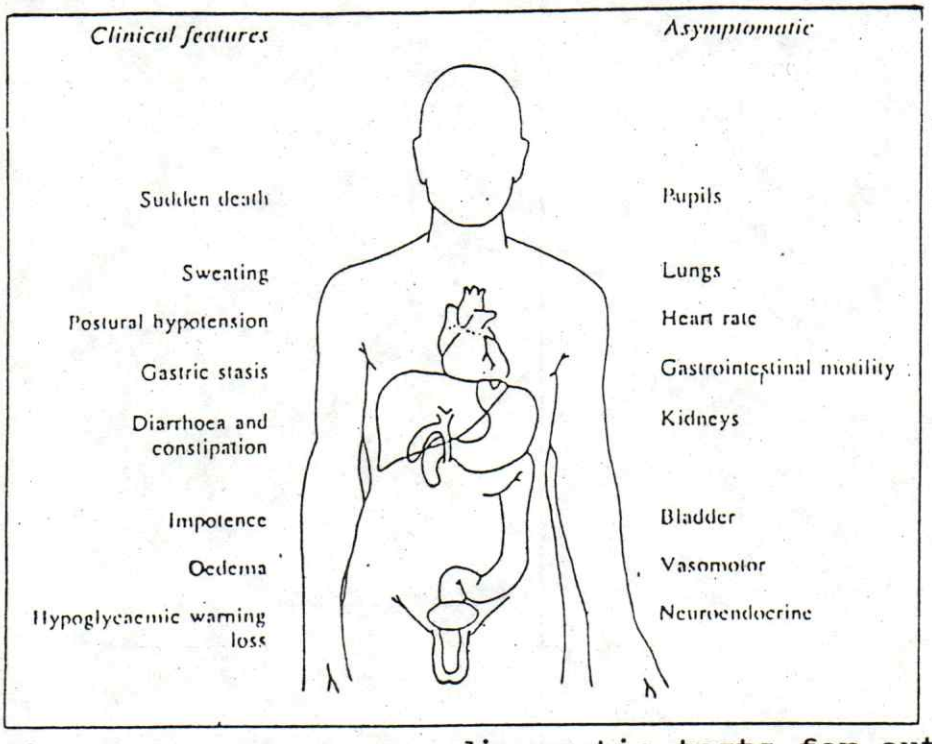
The diversity of microscopic changes have been observed in peripheral nerves from human and experimental diabetes. Schwann cell abnormalities include segmental demyelination and thickening of the basal lamina. Neuronal alterations include axonal degeneration occurring early and preceding demyelination in experimental diabetes. The axonal loss affects myelinated and unmyelinated fibers, especially more distally. Sural nerve biopsies from diabetic subjects with painful peripheral or autonomic neuropathy showed a relatively greater loss of small myelinated and unmyelinated axons. Autonomic nerves have been less commonly studied in human diabetes. A variety of structural changes may occur in sympathetic ganglia and a recent report described in filtration by mononuclear cells suggesting immunologic activity. (*8*)

Manifestation of Diabetic Autonomic Neuropathy

DAN can be asymptomatic, and discovered after several test of autonomic function. Asymptomatic of **DAN** could happen for several years, insidious onset, and usually slowly pro-

gressive manner and tend to become irreversible. (17)
That **AN** is generalized disorder has received frequent confirmation, notably in recent observations of cardiovascular reflex dysfunction in diabetic patient with abnormal esophageal motility, delayed gastric emptying, pupillary dysreflexia, augmented ocular tone and abnormal neuroendocrine responses. (9.15)

Syndrome of Diabetic Autonomic Neuropathy.



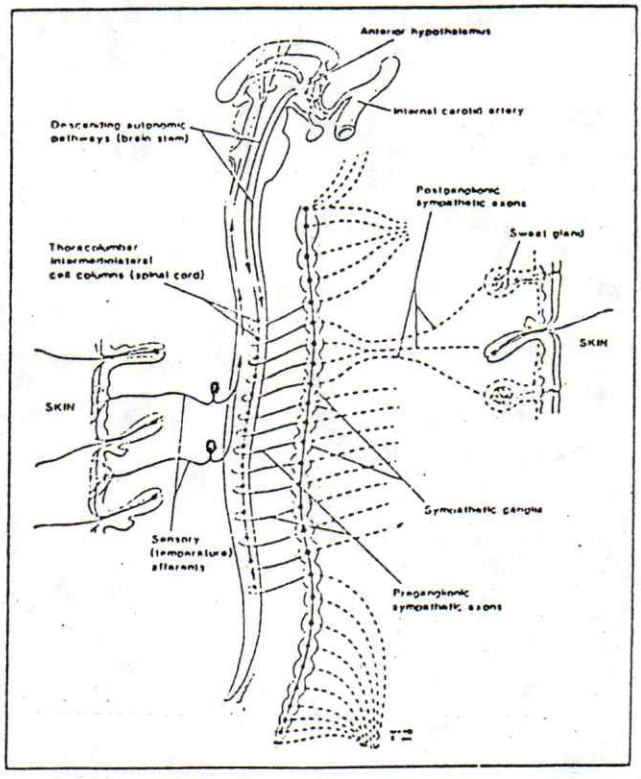
There are some manner diagnostic tests for autonomic function.

Test of autonomic function (14) :

Cardiovascular	Parasympathetic	Sympathetic
• Sinus arrythmia	✓	
• Lying and standing blood pressure		✓
• Expired to inspired R-R interval ratio	✓	
• Valsalva response	✓	
Pupillary		
• Dark adapted pupil diameter		✓
• Light reflex	✓	
Gastric		
• Radioisotope test meal	✓	
Peripheral		
• Galvanic skin response		✓ (cholinergic)
• Axon reflex		✓

Sympathetic sudomotor function in diabetic neuropathy.

Disorders of sweating due to degeneration of post ganglionic sudomotor axons are common expression of **DAN.** Symptoms include hyperhidrosis of the head and chest and heat intolerance with distal anhidrosis, many factors influence sweating depend on not only the integrity of the same post ganglionic skin sympathetic nerves and sweats gland, but also the preganglionic thoracolumbar sympathetic fibers and paravertebral chain ganglia and central autonomic pathway descending from the thermoregulatory integrative center in the hypothalamus, temperature sensitive afferent pathways from the skin and in the spinal cord also influence sweating.(*10,12*)



There are many ways to observe the sweats gland activity from traditional to computerized analysis such as:

In 1945 Rundles and Roth and associates using a heat cradle and cobalt chloride powder on the skin as a sweat indicator.

In Mayo thermoregulatory laboratory is modification of Guttmann's quinizarin sweat test using of indicator powder mixture that consist of Alizarin red S (50 g), sodium carbonate (50 g) and cornstarch (100 g), a 1 : 1 : 2. Overheat infrared heaters maintain the skin temperature between 38.5^0 and 39.5^0 C . Each patient's sweat distributes dark purple in the sweating areas and light orange in anhidrotic areas. (*10*)

The silatic imprint technique, its sensivity and accuracy have been enhanced by the computerized analysis of the molds, had been reported by Kennedy W et all in 1989. The number of sweat gland activated was determined by counting the droplet impression under a dissecting microscope. (*12*)

Although test for abnormalities of the autonomic nervous system with few exceptions, such as testing examination of the skin for abnormalities of color and sweating, the neurologist tend not to be precise in evaluating, the function of autonomic nervous system, nonetheless several simple tests can be used to confirm clinical impressions. (*1*)Beside simple, well validated and non invasive test except using cardiovascular reflexes, now have been refined for assessing autonomic nerve damage other simple tests involving sudomotor function are being developed.

From previous study by Rundles in 1945 demonstrated decreased to absent sweat activity in the distal extremities of 11 of 13 symptomatic patients studied. Roth and associated found that 29 Of 40 patients with diabetes had an abnormal sweating in 74 % of patients with diabetes, ranging from patchy hypohidrosis of the feet to loss of sweating in all four extremities (the trunk was immersed in a hot bath and therefore not examined). Fealey R D et all performed Thermoregulatory sweat test (TST) 48 (94 %) had unequivocal abnormalities on TST, pathologic loss of sweating occurred distally in 65 %, segmentally in 25 %, and only in isolated dermatomes in 25 % of patients had a combination of two or more patterns global anhidrosis was noted in eight patients

(16 %) (*10*)

Pattern of abnormalities relating to autonomic neuropathy out side the cardiovascular system are beginning to be studied. Guy et al have recently observed thermal abnormalities in the feet occurring before abnormal cardiovascular reflexes, which in turn preceded abnormal thermal tests in the hand sweat tests in the feet may be abnormal in the presence of normal heart rate tests.

The rational for our study was twofold : 1. to provide a comprehensive review of our experiences with perspiration test of sweating disturbances related to diabetic neuropathy. 2. To relate perspiration test abnormalities to signs and symptoms of patients and to the result of other tests based on blood pressure (Schellong's test) for detected postural hypotension using a cuff sphygnomanometer, and a fall is systolic blood pressure of 30 mm Hg or more, upon standing is regarded as significant. (Normal : blood pressure systolic fall $\leq$ 10. Abnormal : blood pressure systolic fall $\geq$ 30, Borderline : Blood Pressure fall between that range) This is one of the simplest tests to assess possible autonomic neuropathy.

Subjects and methods

A total of 30 patients with diabetes mellitus, aged 51 to 73 years (mean 63.43) and duration of disease for 4 to 22 years (mean 10.20 years) were evaluated. Consist of 12 females and 18 males. Included in this study were out patients diabetic in Dr Soetomo Hospital Surabaya, Both of department of Neurology and Diabetic department of Internal Medicine had a detailed medical and examination for disclosed no other potential cause of neuropathy. Each patient was also evaluated clinically for sign and symptoms of autonomic dysfunction. The autonomic nervous system was clinically tested by comparing lying and standing blood pressure measurement, after lying on 25 minutes and standing on 3 minutes, and abnormal result being fall of 30 mm Hg or more

in the systolic pressure. (5) Beside by perspiration test as one of the simple methods for measuring sweat gland activity. The methods of color determination of sweating by iodine solution (mixture of iodine 5 g, alcohol 300 ml, ricini's oil 30 ml) is painted on the skin and the printed areas are dusted with starch powder, which turn bluish black in the presence of iodine and moisture. Diaphoretic procedure or heat sweating is produced by used of external heat after the ingestion of hot water and aspirin 1 gram. Large cradles are placed over the patient, and the open ends covered with blankets.

Statistical analysis

The statistical analysis was primarily of descriptive nature. And we tried to analyze the comparison between perspiration test with schellong test, symptom of **DAN** with the result of perspiration test, duration of diabetes with the result of perspiration test was made by Chi square test.

Results

In the periods February 1991 - June 1991, 30 patients with Diabetic neuropathy were admitted to our neurological department at Dr Soetomo Hospital. Among these patients, 12 were females and 18 were males; Their ages ranged from 51 to 73 years, with mean age of 63.4 ± 5.8, and duration of disease from 4 to 22 years, with mean duration of 10.2 ± 4.5

Table 1 : Age and sex distribution

Table 1: Age and sex distribution

Age Range (Years)	Group Sex		Total
	Male	Female	
50 - 54	1	1	2
55 - 59	3	2	5
60 - 64	5	5	10
65 - 69	4	3	7
> 70	5	1	6
Total	18	12	30

Mean age of 63.4 ± 5.8

Table 2: Relation between duration of disease and sex

Duration (years)	Group sex		Total
	Male	Female	
0 - 4	2	1	3
5 - 9	10	4	14
10 - 14	5	4	9
15 - 19	1	1	2
> 20	-	2	2
Total	18	12	30

Mean duration of 10.2 ± 4.5

Table 3: Result of perspiration

Perspiration	Group sex		Total
	Male	Female	
Normal	4	1	5 (17 %)
Abnormal	14	11	25 (83 %)
Total	18	12	30

Table 4: Age and perspiration abnormalities

Age Range (Years)	Group Sex		Total
	Males	Female	
50 - 54	1	1	2
55 - 59	3	2	5
60 - 64	2	5	7
65 - 69	3	2	5
> 70	5	1	6
Total	14	11	25

There are 5 patients with normal perspiration consist of 4 males and 1 female, with age were 61 years(M), 62 years (M), 63 years (M), 67 years (M), and 68 years (F). And duration of disease in normal perspiration were 4 years, 7 years, 9 years, 11 years, 12 years.

Table 5: Sweat distribution patterns

Patterns	Group sex		Total
	Male	Female	
Normal	4	1	5 (17 %)
Distal Anhidrosis	7	4	11 (37 %)
Segmental -- --	3	3	6 (20 %)
Focal sweat loss	4	2	6 (20 %)
Global Anhidrosis	-	2	2 (6 %)
Total	18	12	30

A Normal : the pattern involve no areas of reduced sweating or only minor area of anhidrosis.

Distal Anhidrosis was characterized by sweat loss greatest in the fingers, the legs below the knee, and the anterior aspect of abdomen

Segmental Anhidrosis involved large contiguous zones of the body surface bordered by areas of normal sweating.

Focal sweat loss was confined to small areas in the distribution of isolated dermatomes or peripheral nerves.

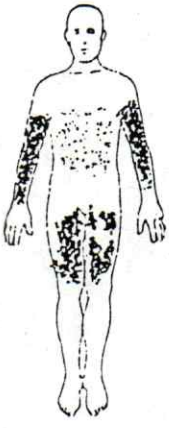
Global Anhidrosis occurred, when more than 80% of body surface was affected.

Segmental abnormalities were most often asymmetric and associated with distal loss of sweating.
Focal anhidrosis was always asymmetric, the dry zone often surrounded by intense sweating.

Case no: 6

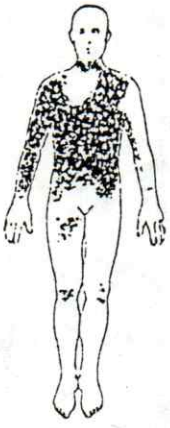
normal

Case no: 1



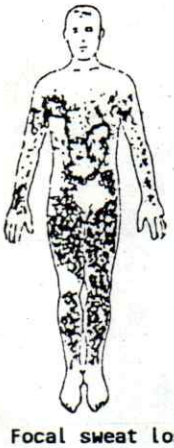
distal anhidrosis

Case no: 4



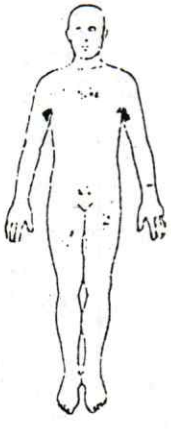
segmental anhidrosis

Case no: 14



Focal sweat loss

Case no : 23 ---- female , 69 years old duration of disease 14 years,---- schellong's test borderline Abn



Global anhidrosis

Cross tab / Chi square test.

Comparison of perspiration abnormalities and clinical symptom.

Perspiration / Clinical symptom	Normal	Abnormal	Total
Symptomatic	3	20	23
Asymptomatic	2	5	7
Total	5	25	30

Chi square with continuity correction factor = 0.149
Prob:0.6994
Chi Square without continuity correction factor = 0.932
Prob: 0.3344
DF = 1
Fisher exact probability : lower tail = 0.3289, uppertail =0.9321
Unproven comparison between perspiration abnormalities and clinical symptom.
Asymptomatic : there were not clinical symptoms of cardiovascular system, gastrointestinal system, genitourinary system, thermoregulatory sweating system.
Symptomatic : where there were ones or more of clinical symptoms.

Cross tab / Chi square test
Comparison of perspiration abnormalities and Schellong test

Schellong / Perspiration	Normal	Abnormal	Total
Normal	4	1	5
Abnormal	20	5	25
Total	24	6	30

Chi square with continuity correction factor : 0.375 Prob: 0.5403
Chi square without continuity correction factor : 0.000
Prob: 1.000

DF = 1
Fisher exact probability : lower tail: 0.7017 Upper tail:0.7457
Unproven comparison between perspiration abnormalities and schellong test.

Cross tab / Chi square test
Duration of disease and perspiration abnormalities.

Perspiration Duration (Years)	Normal	Abnormal	Total
0 - 4	1	2	3
5 - 9	2	12	14
>10	2	11	13
Total	5	25	30

Chi square = 0.673 DF = 2 Prob: 0.7144
Unproven comparison between duration of disease and perspiration abnormalities.

Discussion

Perspiration test abnormalities were observed in 25 of 30 patients (83 %) with diabetes who had findings suggestive of neuropathy, Compared with previous studies by Fealey R D et all were observed in 48 of 51 patients (94 %). It mean that perspiration test can be done as one's of the simplest testing of detected autonomic function in patient

with diabetes. Perspiration test as cheap examination method can be done at another small hospital in Indonesia. Although it was not comfortable for patient, and needed longer time to do it.

Schellong's test was less shown of abnormalities of detected autonomic function, in this study was reported schellong's test was normal in 24 patients, borderline in 4 patients and abnormal in 2 patients.

The perspiration test allowed visualization of the often patchy and multifocal nerve involvement, this useful information concerning with the distribution of neuropathy was provided. Finally although perspiration test only a qualitative, at one time enable clinicians to monitor progression of disease and response to treatment.(*10*)

Conclusion

This study demonstrated the high frequency of perspiration test sweating abnormalities in a well characterized group of patients with diabetes, who had sign and symptoms of neuropathy. The pattern of anhidrosis can be suggestive of certain disorder neuropathic syndromes.

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