



THE JOURNAL OF CLINICAL PSYCHIATRY

Supplementary Material

Article Title: New Evidence for the Involvement of Mitochondrial Inheritance in Schizophrenia: Results From a Cross-Sectional Study Evaluating the Risk of Illness in Relatives of Schizophrenia Patients

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DOI Number: 10.4088/JCP.10m06718

List of Supplementary Material for the article

1. [Workflow of data collection](#)
2. [Guide and data sheet for conducting direct interviews with patients](#)
3. [Guide and data sheet for conducting direct interviews with relatives](#)
4. [Questionnaire](#)
5. [Annex 1: Data sheet from patients](#)
6. [Annex 2: Data sheet from relatives](#)
7. [Annex 3: Table 1](#)
8. [Annex 3: Table 2](#)
9. [Annex 3: Table 3](#)

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Workflow of data collection

1. Identification of a clinically stable patient

A. Direct interview of patient

2. Explanation of the purpose of the study. Obtaining of Informed Consent
3. Obtaining clinical, socio-demographic and drug consumption data
4. Obtaining information regarding schizophrenia or other psychotic disorders present in relatives
5. Obtaining information regarding other psychiatric disorders present in relatives

B. Direct interview of relative(s)

6. Explanation of the purpose of the study. Obtaining of Informed Consent
7. Obtaining clinical data about onset and evolution of illness of the patient
8. Build-up of the pedigree
9. Obtaining information regarding schizophrenia or other psychotic disorders present in the pedigree
10. Obtaining information regarding other psychiatric disorders present in the pedigree
11. Obtaining information regarding conditions related to mitochondrial disorders present in the pedigree

C. Contrasting data

12. Comparison of data retrieved from the patient and relatives
13. Confirming schizophrenia or psychotic disorders in relatives through medical records

Guide and data sheet for conducting direct interviews with patients

ANNEX 1: DATA SHEET FROM PATIENTS (regarding psychiatric disorders)

A.4.

The following guide should be used to obtain information regarding schizophrenia or other psychotic disorders that might be present in relatives.

Please tell me whether anyone on the list that I will mention has ever had schizophrenia or other psychotic disorders. Read slowly and in the given order for every possible relative.

A.5.

Now please tell me whether anyone on the list that I will repeat has ever had a serious mental illness, emotional problem or nervous breakdown. Read again slowly and in the given order for each relative.

The following questions should be used either as a general comment (if the patient did not identify any psychiatric problem/diagnoses in relatives) or to investigate the specific psychiatric diagnoses (if there is any evidence of psychopathology in a specific relative). Also, the interviewer should ask clarifying questions to identify the probable psychiatric diagnosis of the relative.

1. Has [any of your relatives/ (he/she)] ever seen a psychiatrist, psychologist or other health professional for a psychological or emotional problem?
2. What kind of problem(s)?
3. Was he/she treated for them?
4. Has he/she received pharmacological or psychological treatment?
5. Was he/she hospitalized?
6. How many times?
7. Do you know whether he/she has a specific psychiatric diagnosis?
8. Did he/she ever feel sad, blue, depressed or tired or have less energy?
9. Did he/she ever exhibit an abnormally elevated or irritable mood, arousal, energy level or reduced need for sleep?
10. Did he/she ever have effects of anxiety such as heart palpitations, chest pain, muscle weakness and tension, nausea, shortness of breath, stomach ache or headache? Has he/she ever experienced a panic attack?
11. Did he/she ever have sensory perception (hearing, sight, smell, taste or touch) in the absence of external stimuli, extravagant or unreal beliefs or conduct disorganization?

Guide and data sheet for conducting direct interviews with relatives

[ANNEX 2: DATA SHEET FROM RELATIVES \(regarding psychiatric disorders\)](#)

[ANNEX 3: QUESTIONNAIRE AND DATA SHEET FROM RELATIVES \(regarding conditions that are related to mitochondrial disorders\)](#)

B.8.

Construct a family tree including all possible relatives of the patient. Write the first name of each relative. Begin by asking about the kinship of the interviewed relative with the patient. Follow with the patient's father and mother, brother(s) and sister(s), son(s) and daughter(s), paternal grandfather and grandmother, maternal grandfather and grandmother, nephews and nieces, uncles and aunts and cousins.

B.9.

The following guide should be used to obtain information about the patient's family. The interviewer should be flexible in deciding what to ask and whether it is necessary to continue the interview with respect to a particular family member. The questions should be formulated for each relative to ensure that none is omitted. Obviously, use the appropriate name and gender. Start with first-degree relatives.

Please tell me whether any of the members of this pedigree has ever had schizophrenia or any other psychotic disorder.

Start asking about the patient's father and mother, then his/her brothers and sisters, sons and daughters, paternal grandfather and grandmother, maternal grandfather and grandmother, nephews and nieces, uncles and aunts and cousins.

B.10.

Now please tell me whether any of the pedigree members has ever had a serious mental illness, emotional problem or nervous breakdown?

The following questions should be used either for a general comment (if the relative does not identify any psychiatric problem/diagnoses in his/her relatives) or to investigate the specific psychiatric diagnoses (if there is evidence of psychopathology in a specific relative).

1. Has [any of your relatives/ (he/she)] ever seen a psychiatrist, psychologist or other health professional for a psychological or emotional problem?
2. What kind of problem?
3. Were he/she treated for the problem?
4. Has he/she received pharmacological or psychological treatment?
5. Were he/(she hospitalized?
6. How many times?
7. Do you know whether he/she has a specific psychiatric diagnosis?
8. Did he/she ever feel sad, blue, depressed or tired or have less energy?
9. Did he/she ever exhibit an abnormally elevated or irritable mood, arousal, energy level or reduced need for sleep?
10. Did he/she ever have effects of anxiety such as heart palpitations, chest pain, muscle weakness and tension, nausea, shortness of breath, stomach ache or headaches? Has he/she ever experienced a panic attack?
11. Did he/she ever have sensory perception (hearing, sight, smell, taste or touch) in the absence of external stimuli, extravagant or unreal beliefs or conduct disorganization?

B.11.

The following questionnaire should be used to obtain information regarding conditions related to mitochondrial disorders present in the pedigree. Start asking the interviewed relative about the presence of the conditions in themselves, the patient and other biological relatives (follow this order: the patient's father and mother, brothers and sisters, sons and daughters, paternal grandfather and grandmother, maternal grandfather and grandmother, nephews and nieces, uncles and aunts and cousins). Mark with a cross in the questionnaire table if the condition is present in the patient and/or the interviewed relative. If they are present in other relatives, record this information (the corresponding number of the condition) in the corresponding tables in ANNEX 3.

QUESTIONNAIRE

		Patient	Relative	
1	What is your relationship with the patient? _____	XXXXXX		
2	What is your current age? ____/____years. What is your birth date?_____/_____	XXXXXX	XXXX	XXXX
HEADACHES				
3	Have you suffered from ongoing headaches (including at least 5)? If no, skip to question #4.			
	If so, were the headaches usually associated with any of the following:	XXXXXX	XXXX	XXXX
3a	Lasting between 4 and 72 hours each?			
3b	Occurring only on one side of your head?			
3c	Pulsating or throbbing?			
3d	Severe enough to change your usual daily activity?			
3e	Aggravated by walking on stairs or other similar routines?			
3f	Nausea and/or vomiting during the headache?			
3g	Increased pain with bright lights during the headache?			
3h	Increased pain with loud noises during the headache?			
3i	In the hour just prior to the onset of the headaches, did you experience any of the following: visual changes including flashes of light, tingling, numbness, weakness or speech difficulty?			
4	Have you ever been diagnosed with "migraine" by a physician?			
BOWEL FUNCTION				
5	Have you had ongoing problems with constipation for which you were treated with medications or diet?			
6	Have you had ongoing problems with diarrhea for which you were treated with medications or diet?			
7	In the last year, have you had abdominal pain or discomfort for at least 12 weeks (not necessarily in a row)? If no, skip to question #8.			
	If so, was it associated with any of the following:	XXXXXX	XXXX	XXXX
7a	Change in stool consistency (softer, harder)?			
7b	Change in stooling frequency (more or less often)?			
7c	Relieved with defecation (stooling)?			
8	Have you ever been diagnosed with "irritable bowel" by a physician?			
9	Has a small portion of food made you feel full right away?			
10	Have you ever been diagnosed with "delayed gastric emptying" by a physician?			
11	Have you suffered from 5 or more similar episodes of nausea and vomiting? If no, skip to #12.			
11a	During these episodes, were you lethargic or sleepy?			
11b	Did the nausea and vomiting essentially go away between episodes?			
12	Have you frequently suffered from motion sickness in cars, boats or planes (at least 25% of trips)?			
SOFT TISSUES & FATIGUE				
13	At any time in your life, did you experience severe fatigue for 6 months or longer? If no, skip to #14.			
13a	Did the fatigue affect both physical and mental function?			
13b	Was the fatigue present at least half (50%) of the time?			
13c	Did you find it difficult to walk 5 blocks?			
13d	Was the fatigue severe enough to interfere with work or recreational activities?			
14	Have you ever been diagnosed with "chronic fatigue" or "Epstein-Barr" by a physician?			
15	Have you ever been diagnosed with "fibromyalgia" by a physician?			
16	Have you ever had any troublesome color change or swelling of any part of your body?			

17	Have your hands and/or feet frequently felt cold?			
18	Have you ever suffered from frequent and painful muscle cramps?			
18a	If you answered yes to #16, #17, or #18: At any given time, did it affect one side of the body more than the other?			
19	Have you ever been diagnosed with "Raynaud's" by a physician?			
20	Have you ever been diagnosed with "arthritis" by a physician?			
	NERVES & BRAIN			
21	Have you ever had fainting spells?			
22	Have you ever had droopy eyelids?			
23	Have you ever had a seizure?			
24	Have you had frequent unexplained high or low body temperatures as measured by a thermometer?			
25	Have you had muscle weakness or muscle fatigue on exertion?			
26	Were you ever diagnosed with mental retardation?			
27	Have you ever been diagnosed with "attention deficit disorder" with or without "hyperactivity" ("ADD" or "ADHD") by a professional such as a physician or psychologist?			
28	Have you ever been tested and found to have a learning disability, including dyslexia?			
29	Have you ever been diagnosed with "autism", "autistic features" or "Asperger syndrome" by a professional such as a physician or a psychologist?			
	MENTAL HEALTH			
30	Have you ever been diagnosed with "anxiety" or "anxiety disorder" by a professional such as a physician or a psychologist? If no, skip to #31.			
30a	Were you treated with medications for your anxiety?			
31	Have you ever been diagnosed with "schizophrenia" by a professional such as a physician or a psychologist?			
32	Have you ever had times when you had a lot of energy during which you did things that you regretted later (mania)?			
33	Have you ever been diagnosed with "bipolar disorder" or "manic-depression" by a professional such as a physician or a psychologist?			
34	Have you ever been diagnosed with "depression" by a professional such as a physician or a psychologist? If no, skip to #35.			
34a	Were you treated with medications for your depression?			
34b	Did your symptoms of depression last for more than 6 months?			
	While you were depressed, did you experience any of the following nearly every day:	XXXXXX	XXXX	XXXX
34c	Depressed mood (sadness)?			
34d	Less interest or pleasure in nearly all activities?			
34e	Substantial change in appetite and/or weight?			
34f	Substantially more or less sleep?			
34g	Faster or slower activity levels as observed by others?			
34h	Tiredness or loss of energy?			
34i	Felt worthless or inappropriately guilty?			
34j	Trouble thinking or concentrating?			
35	Have you ever been diagnosed with "panic attacks" by a professional such as a physician or a psychologist? If no, skip to #36.			
35a	Were you treated with medications for your panic attacks?			
	EARS & EYES			
36	Have you ever suffered from hearing loss? If no, skip to #37.			
36a	If so, how old were you when hearing loss started? _____	XXXXXX	XXXX	XXXX
36b	Was the hearing loss worse in one ear compared to the other?			
37	Have you ever heard frequent ringing in your ears (tinnitus)?			
38	Have you had substantial problems with vision that was not correctable by glasses or contacts?			

39	Are you bothered by bright lights more than other people (not only during headaches)?			
40	Have you ever had cross-eyedness (strabismus)?			
	HORMONES			
41	Do you generally have problems if you miss a meal? If no, skip to #42.			
41a	If so, what problems?_____	XXXXXX	XXXX	XXXX
42	Have you ever had hypoglycemia documented by a low blood sugar level?			
43	Have you ever been diagnosed with "hypothyroidism" by a physician?			
44	Have you ever been diagnosed with "diabetes" by a physician?			
45	Have you ever had growth hormone deficiency documented by laboratory testing?			
	HEART & BLOOD VESSELS			
46	Have you ever suffered a heart attack?			
47	Have you ever suffered a stroke?			
48	Have you frequently felt your heart racing, even when you were not anxious?			
49	Have you ever been diagnosed with "tachycardia" or an abnormally high heart rate by a physician?			
50	Have you ever been diagnosed with "cardiomyopathy" by a physician?			
51	Have you ever been treated with diet or medications for high blood pressure?			
52	Have you ever been told your cholesterol level was high?			
	OTHER			
53	Other than infections, have you ever had any kidney disease?			
54	On most nights, do you need to get out of bed in the middle of the night to urinate?			
55	Have you ever had cancer?			
56	Were you born with a birth defect that required therapy or surgery? If no, skip to #57.			
56a	If so, what birth defect?_____	XXXXXX	XXXX	XXXX
57	Have you ever been diagnosed with an immunodeficiency (decreased immune system) or have had severe or unusual infections?			
58	Have you ever been pregnant? If no, skip to #59			
58a	During any pregnancy, did you experience a substantial amount of nausea or vomiting? If no, skip to #59.			
58b	Was intravenous (iv) fluid needed because of nausea or vomiting?			
59	Have you ever had any significant medical problems not asked in this questionnaire? If no, skip to #60.			
59a	If so, what problems?_____	XXXXXX XXXXXX	XXXX XXXX	XXXX XXXX
60	Did any children in your family die suddenly from unknown causes? If no, skip to the end.			
60a	If so, at what age (months or years)?_____	XXXXXX	XXXX	XXXX
60b	How was this child related to you?_____	XXXXXX	XXXX	XXXX
60c	Was a diagnosis of sudden infant death syndrome (SIDS) or probable SIDS given?			

ANNEX 1:

Patient code: _____	DATA SHEET FROM PATIENTS		
Kinship	Schizophrenia (⊗ yes/ __ no)	Other psychotic disorder (⊗ yes/ __ no) Specify	Other psychiatric disorders (⊗ yes/ __ no) Specify
Father			
Mother			
Brother			
Sister			
Son ¹			
Daughter ¹			
Maternal grand-father			
Maternal grand-mother			
Paternal grand-father			
Paternal grand-mother			
Nephew (son of a brother) ¹			
Niece (daughter of a brother) ¹			
Nephew (son of a sister) ¹			
Niece (daughter of a sister) ¹			
Paternal uncle ¹			
Paternal aunt ¹			
Maternal uncle ¹			
Maternal aunt ¹			
Son of a maternal aunt ¹			
Daughter of a maternal aunt ¹			
Son of a maternal uncle ¹			
Daughter of a maternal uncle ¹			
Son of a paternal aunt ¹			
Daughter of a paternal aunt ¹			
Son of a paternal uncle ¹			
Daughter of a maternal uncle ¹			

¹ Indicate the number of individuals if more than one.

ANNEX 2:

Patient code: _____	DATA SHEET FROM RELATIVES (regarding psychiatric disorders)		
Kinship	Schizophrenia (⊗ yes/ __ no)	Other psychotic disorder (⊗ yes/ __ no) Specify	Other psychiatric disorders (⊗ yes/ __ no) Specify
Father			
Mother			
Brother			
Sister			
Son ¹			
Daughter ¹			
Maternal grand-father			
Maternal grand-mother			
Paternal grand-father			
Paternal grand-mother			
Nephew (son of a brother) ¹			
Niece (daughter of a brother) ¹			
Nephew (son of a sister) ¹			
Niece (daughter of a sister) ¹			
Paternal uncle ¹			
Paternal aunt ¹			
Maternal uncle ¹			
Maternal aunt ¹			
Son of a maternal aunt ¹			
Daughter of a maternal aunt ¹			
Son of a maternal uncle ¹			
Daughter of a maternal uncle ¹			
Son of a paternal aunt ¹			
Daughter of a paternal aunt ¹			
Son of a paternal uncle ¹			
Daughter of a maternal uncle ¹			

¹ Indicate the number of individuals if more than one.

ANNEX 3: Table 1

DATA SHEET FROM RELATIVES (regarding conditions related to mitochondrial disorders)								
Patient code: _____	MATERNAL RELATIVES							
Condition	Grand-father	Grand-mother	Uncle ¹	Aunt ¹	Son of a maternal aunt ¹	Daughter of a maternal aunt ¹	Son of a maternal uncle ¹	Daughter of a maternal uncle ¹

¹ Indicate the number of individuals if more than one.

ANNEX 3: Table 2

DATA SHEET FROM RELATIVES (regarding conditions related to mitochondrial disorders)								
Patient code: _____	PATERNAL RELATIVES							
Condition	Grand-father	Grand-mother	Uncle ¹	Aunt ¹	Son of a paternal aunt ¹	Daughter of a paternal aunt ¹	Son of a paternal uncle ¹	Daughter of a paternal uncle ¹

¹ Indicate the number of individuals if more than one.

ANNEX 3: Table 3

DATA SHEET FROM RELATIVES (regarding conditions related to mitochondrial disorders)										
Patient code: _____	FIRST-DEGREE RELATIVES						OTHER			
Condition	Mother	Father	Brother ¹	Sister ¹	Son ¹	Daughter ¹	Nephew (son of a brother) ¹	Niece (daughter of a brother) ¹	Nephew (son of a sister) ¹	Niece (daughter of a sister) ¹

¹ Indicate the number of individuals if more than one.