P+A+MSA CLINIC

Parkinson's Plus
Ataxia
Multiple System Atrophy

HARVARD MEDICAL SCHOOL

BRIGHAM AND WOMEN'S HOSPITAL

Sporadic Ataxia and MSAc

Netter Images

Vikram Khurana, MD PhD

khuranalab.bwh.harvard.edu

SPEAKER DISCLOSURE: VIKRAM KHURANA MD PHD

- Scientific co-founder and Equity Holder.

National Ataxia Foundation

DISCLAIMER

- The information provided by speakers in any presentation made as part of the 2016 NAF Annual Ataxia Conference is for informational use only.
- NAF encourages all attendees to consult with their primary care provider, neurologist, or other health care provider about any advice, exercise, therapies, medication, treatment, nutritional supplement, or regimen that may have been mentioned as part of any presentation.
- Products or services mentioned during these presentations does not imply endorsement by NAF.

Concepts & Definitions

- **HEREDITARY**

  "Runs in families"

  If it affects every generation ("autosomal DOMINANT")

  → *50% chance transmission from a carrier parent*

  If it skips generations ("autosomal RECESSIVE")

  → *25% chance of transmission from two parents who are carriers*

- **SPORADIC**

  SPORADIC does *not* rule out a genetic contribution, but there is no clear transmission between generations

  Multiple genes and/or environmental factors are involved

  20-25% of patients with "sporadic" ataxia have **multiple system atrophy**

- **SECONDARY**

  The ataxia arises secondary to some other non-neurologic process (immune disorder, brain injury, infection, metabolic problem etc.)

Concepts & Definitions

- **SEQUENCING**

  Deciphering the DNA letters that make up the genetic code

- **GENOME**

  3 billion letters (“base pairs”) that make up the *entire* genetic code.

  The genome is divided up into “genes” that provide the roadmap to make our proteins

- **EXOME**

  30 million letters (1%) of the genome that make up the part of a gene that directly leads to protein construction

  We can sequence the exome for **around three to five thousand dollars**

We still don’t know what many variations in the exome or genome actually mean!

Take Home Messages

- **YOU DESERVE A GOOD DIAGNOSIS**

  Diagnosis matters for treatment and to benefit from the rapid advances in the science!

- **FIND CARING PROVIDERS**

  Physicians and allied health professionals who understand your problem and listen to you!

  Think about forming alliances between providers if you live far away from an ataxia center.

  Consider engaging with researchers – cures will only come from a collaboration between patients, physicians and scientists.

SPORADIC ATAXIA

- **No clear family history**

- **Many cases will have genetic contributors that can be found**
  - May be the first family member affected by a *spontaneous gene mutation*
  - May be a combination of genetic mutations that is creating the problem
  - Brent Fogel (JAMA Neurology 2014) – 60% patients have relevant genetic findings!

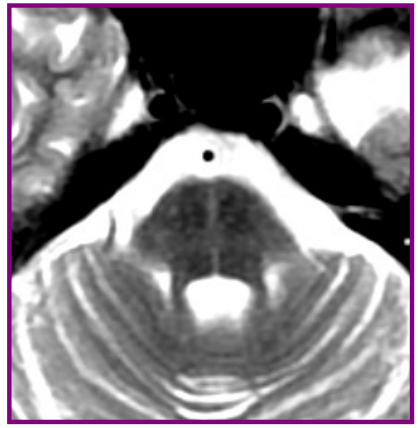
- **20-25% of cases will be MSA**

- **Make sure secondary causes are ruled out!**
  - Immune (celiac, thyroid, GAD, tumor antibodies; “paraneoplastic”)
  - Drugs
  - Heavy Metals
  - Infectious
  - Metabolic

MULTIPLE SYSTEM ATROPHY (MSA)

- **Other names**
  - "Shy Drager" "Striatonigral degeneration" "Olivopontocerebellar Atrophy"
- **Ataxia or Parkinsonism + *Autonomic* symptoms**
  - Ataxia predominates: **MSA type C** "Cerebellar"
    Parkinsonism predominates: **MSA type P** "Parkinsonian"
- **Distinguishing features**

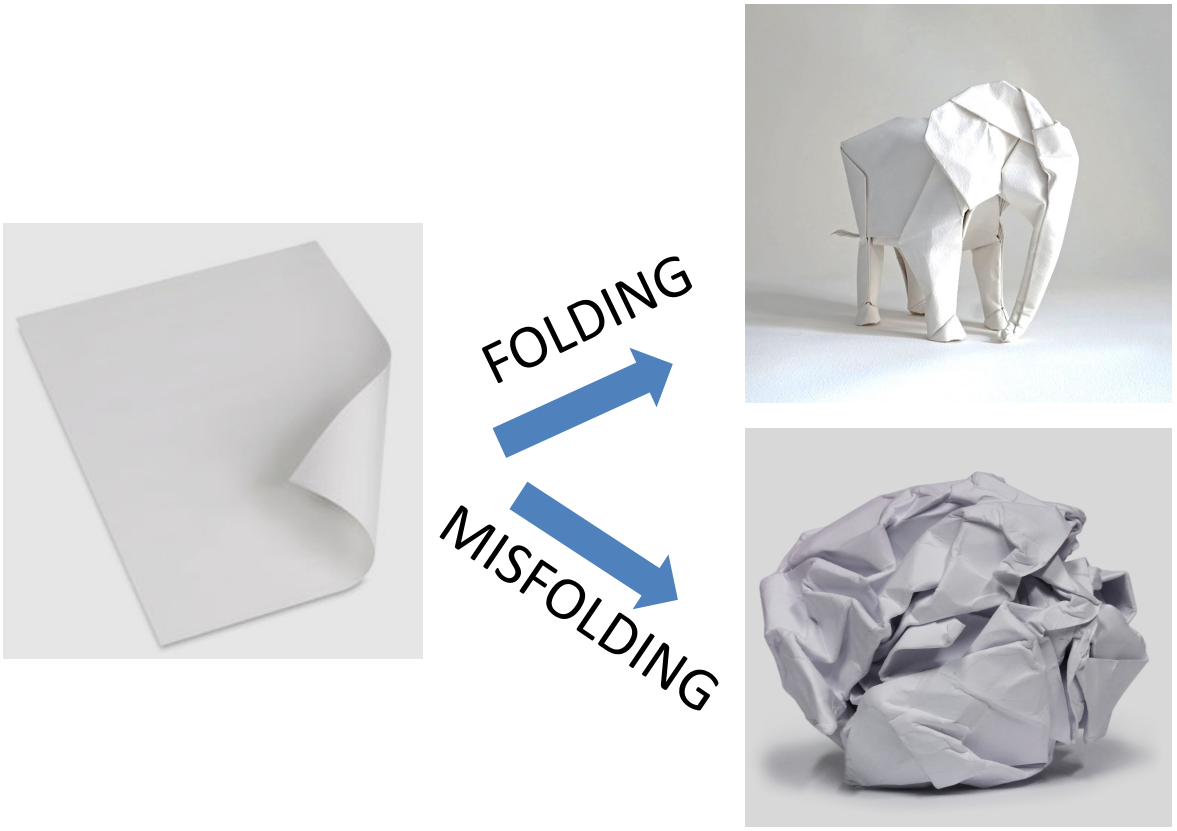
  Early disturbances (REM sleep disorder – thrashing around in sleep, nightmares)
  Autonomic features (bladder, erectile, bowel dysfunction; blood pressure drops)
  Imaging findings

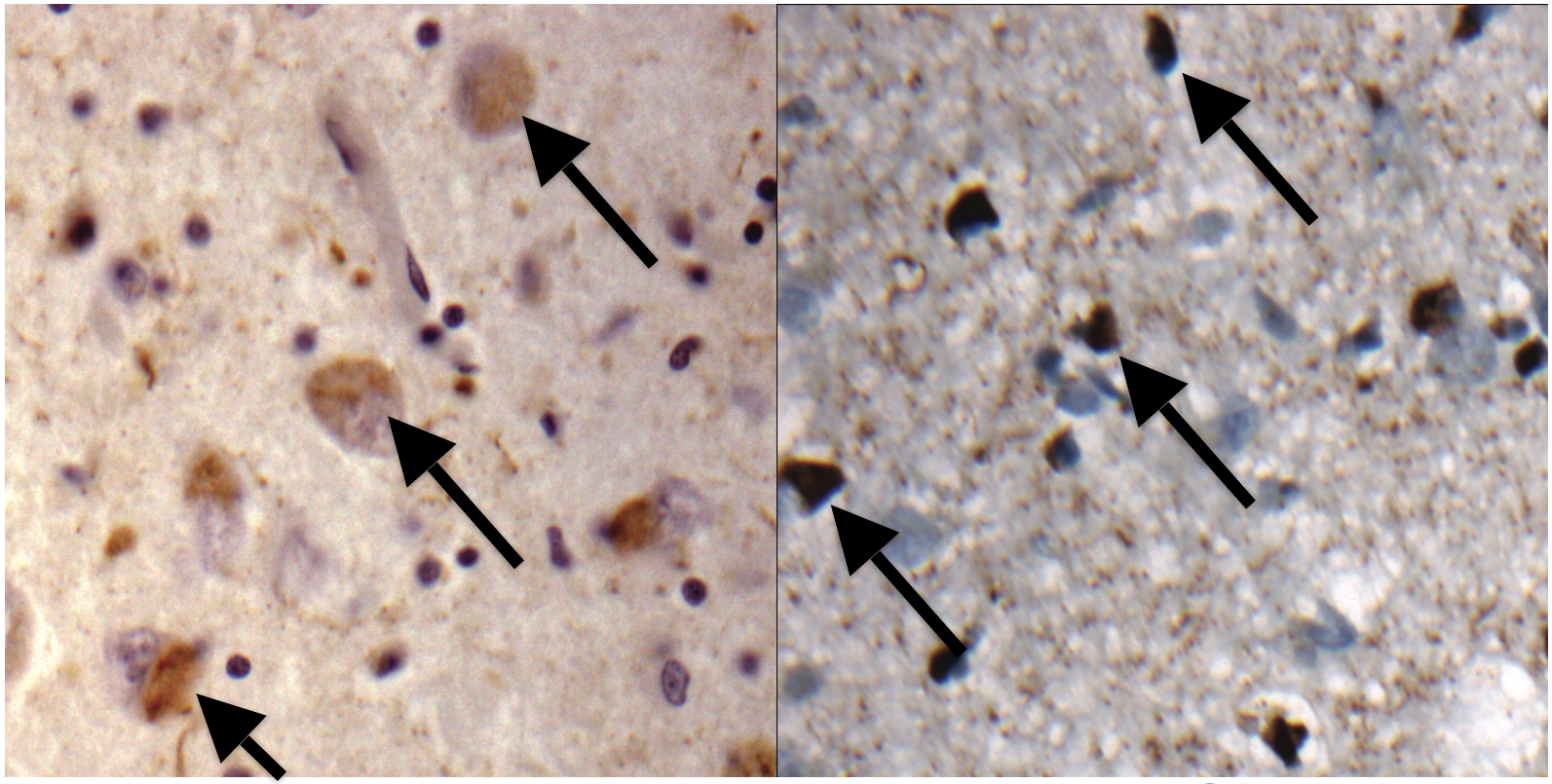


- **Statistics**

  15-50 000 patients in US (probably underdiagnosed)
  Compare to > 1 million patients with Parkinson's disease
  Mean age of onset in 50s

MSA is a protein misfolding disorder





PARKINSON'S MSA

alpha-SYNUCLEIN

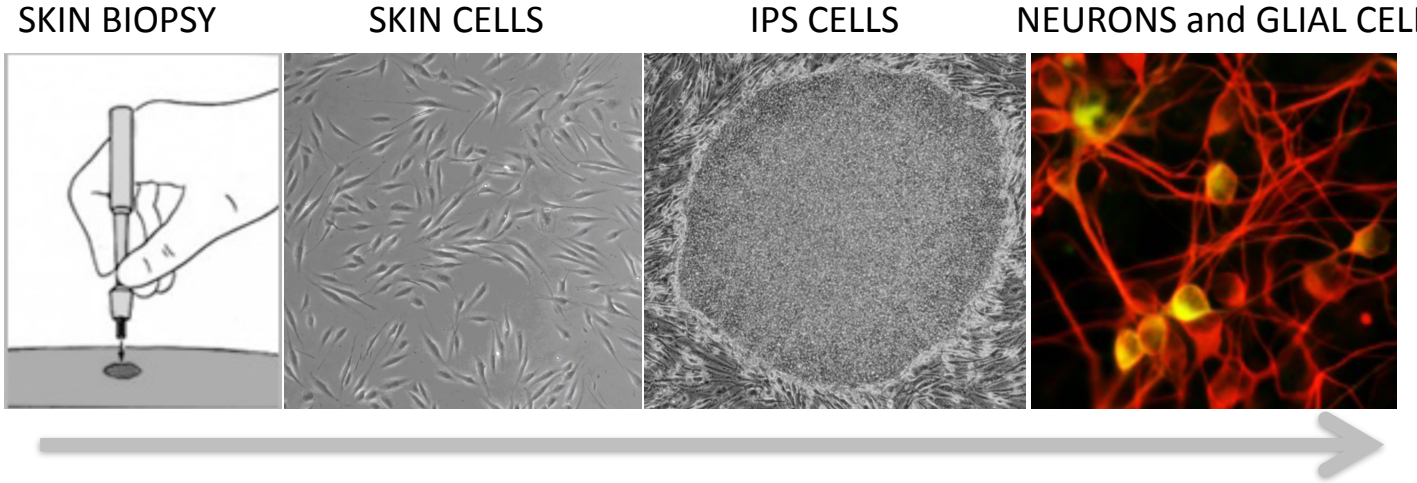
Culprit Protein in Parkinson's and MSA

What does the connection to Parkinson's mean for MSA?

- **Benefits of a ~20years of research into alpha-synuclein**
  - Biology, Biomarkers, Trial Therapies
  - Stem Cell Technologies
- **Development of animal and cellular "models" of MSA**
  - Mouse models of MSA were rapidly developed and characterized
- **MSA offers a tremendous opportunity for the Parkinson's field too**
  - A cohort of patients with a rare disease that has no treatment
  - Allows the Parkinson's field to more easily test anti-synuclein therapies
  - A great example is anti-synuclein antibodies

iPS approach:

Personalizing drugs directed at alpha-synuclein toxicity



"PD or MSA in a dish"

Implications for MSA

1) STEM CELLS (iPSc)

from MSA patients

a) Identify defects
b) Therapeutic testing Biomarker discovery
c) Drug Screening

2) FK506

a) Biomarkers to establish *target engagement*
b) Therapeutic drug trial

Implications for MSA

1) STEM CELLS (iPSc)

from MSA patients

2) FK506

Why a national stem cell bank?

STRENGTH IN NUMBERS

* ***MSA is a "sporadic disease" which means we cannot yet "correct it" genetically in a dish***
* ***Is it one disease or many diseases?***

We need to understand it to effectively treat it

Treatment Considerations

- No established treatments for the ataxia symptom itself
- EXCEPTIONS: episodic ataxia (acetazolamide/diamox, 4-aminopyridine)
- Riluzole is potentially useful and can be tried, but more data is needed
- **BUT symptomatic therapy is available and EFFECTIVE in improving quality of life**
  - * MOOD (SSRIs are mainstay for depression)
  - * REM SLEEP DISORDER (clonazepam is first-line, DA agonists)
  - * RESTLESS LEG SYNDROME (DA agonists, gabapentin, etc.)
  - * PARKINSONISM (carbidopa/levodopa is mainstay)
  - * EPISODIC ATAXIA (acetazolamide, 4-aminopyridine)
  - * FOCAL DYSTONIA (botulinum toxin)
  - * POSTURAL/LIMB KINETIC TREMOR (propanolol, primidone, etc)
  - * URINARY FREQUENCY (anticholinergics, HOB elevation)
  - * CONSTIPATION (conservative, lubiprostone)
  - * ORTHOSTASIS (conservative – elevate head of bed, increase early morning fluid intake, increase salt intake, smaller meals, medications - midodrine, droxidopa, fludrocortisone)
- Vitamin supplements (empiric – coQ10, MVI, vitamins B complex, C, E)
- Mitochondrial "cocktails" (alpha-lipoic acid, carnitine, creatine, riboflavin, thiamine, pyridoxine, selenium)
- **DO NOT UNDERESTIMATE AEROBIC EXERCISE and PHYSICAL THERAPY (eg recumbent bike)**
- SPEECH THERAPY (LSVT, assistive devices, swallow) and OCCUPATIONAL THERAPY