



Opsoclonus Myoclonus Ataxia Family Symposium Outcomes and Transition

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Goals and Objectives

- Understand historical outcome findings for OMA in the short and long term
- Understand different features that might predict outcomes
- Understand the evolution of treatment for OMA and how that might influence outcomes
- Understand the general transition process

Overview

- Outcomes
 - Historical outcomes
 - Current outcomes
- Transition
 - Process description

How do we best assess outcomes in rare diseases?

- Small numbers of patients at single institutions
- No single disease biomarker identified to correlate with outcome
- Evolving treatment plans
- Which outcomes?
 - Short term (e.g. resolution of core OMA symptoms)
 - Long term (e.g. relapses, motor, learning, speech, behavior)
 - Longer term (e.g. functional independence)

Outcome considerations with evolution of treatment

- 1970s-1980s: observation only after resection of the neuroblastoma
- 1980s-1990s: short term treatment with steroids and/or ACTH
- 1990s-2000s: steroids + IVIG
- 2000s-present: steroid + IVIG + other immune modulating agents

What influences short and long term outcome?

- Duration of symptoms? Severity of presentation?
- Gender?
- Presence and/or biology of tumor?
- Spinal fluid results?
- “Aggressiveness” of initial therapy?
- Duration of therapy?
- Occurrence of relapses?

Tumor outcomes – the easier question

- Event-free survival from the neuroblastoma is nearly 100%

Outcome and Prognostic Features in Opsoclonus-Myoclonus Syndrome From Infancy to Adult Life



WHAT'S KNOWN ON THIS SUBJECT: Opsoclonus-myoclonus syndrome (OMS) is a chronic-relapsing and debilitating illness of early childhood that often has an atypical presentation. There is a paucity of data on prognostic factors and long-term outcome of people with OMS beyond childhood into adolescence and adult life.



WHAT THIS STUDY ADDS: Children with severe initial symptoms and those who are very young at disease onset are at particular risk of developing long-term neurologic sequelae. It is important for those affected to be identified early, because they might benefit from new advances in immunomodulating therapy.

abstract

OBJECTIVE: Opsoclonus-myoclonus syndrome (OMS) is a serious and often chronically disabling neurologic illness with onset in early childhood. Our aim was to identify long-term neurologic sequelae of OMS and predictors for disease outcome.

METHODS: We retrospectively assessed the case records of 101 patients diagnosed with OMS over a 53-year period. Clinical data were obtained from medical record review; we documented age at onset,

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KEY WORDS

opsoclonus-myoclonus syndrome, OMS, dancing-eye syndrome, DES

ABBREVIATIONS

OMS—opsoclonus-myoclonus syndrome
IVIg—intravenous immunoglobulin

Dr Brunklaus made substantial contributions to conception, design, acquisition of data, analysis, and interpretation of data and drafted the article; Dr Pohl made substantial contributions to conception, design, and acquisition of data and revised the article critically for important intellectual content; Dr Zuberi made substantial contributions to interpretation of data and revised the article critically for important intellectual content; and Dr deSousa made substantial contributions to conception, design, and interpretation of data and revised the article critically for important intellectual content.

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Outcome and Prognostic Features in Opsoclonus-Myoclonus Syndrome From Infancy to Adult Life

- Statistical review of 101 patients over a 53 year period with OMA to answer:
 - What presenting features predict outcome?
 - Is the disease progressive or static?
- Treatment response graded during 1st 2 weeks of therapy
- Neurological and neuropsychological outcome measured in school-age children with > 3 years of follow-up
 - 73 children with median age of 9 years

Outcome and Prognostic Features in Opsoclonus-Myoclonus Syndrome From Infancy to Adult Life

- Children grouped by outcomes
 - Mild/Moderate course: Single attack or relapsing disease with normal exam between relapses (28 kids)
 - Chronic relapsing disease with residual deficits (45 kids)
- Motor ability, intellectual capacity, speech pathology, and behavior problems were each assessed independently

Outcome and Prognostic Features in Opsoclonus-Myoclonus Syndrome From Infancy to Adult Life

- 87% initial treatment with steroids (prednisolone 53%, corticotrophin 30%)
- 90% responded to some degree within 1 month
- 72% received steroids only
 - 16% steroids plus one other treatment,
 - 12% received no treatment
- Weaning of steroids associated relapse in 82%, and intercurrent illness associated relapse in 87%

Outcome and Prognostic Features in Opsoclonus-Myoclonus Syndrome From Infancy to Adult Life

Long-term Outcome for Patients With OMS

Outcome Measure	n/N (%)
Disease course	
Chronic relapsing	45/73 (61)
Intermediate	23/73 (32)
Monophasic	5/73 (7)
Motor abnormality/ataxia	44/73 (60)
Opsoclonus (intermittent)	10/67 (15)
Speech abnormality	48/73 (66)
Learning disability	37/73 (51)
Behavior problems (ADHD, oppositional, rage)	33/57 (46)
Ongoing medication	10/73 (14)

Average follow-up of 7.3 years (range: 3–32 years)

Outcome and Prognostic Features in Opsoclonus-Myoclonus Syndrome From Infancy to Adult Life

- Severe initial symptoms (i.e. inability to sit or walk independently) were 2.7 times more likely to have a chronic-relapsing course than mild/moderate initial symptoms (i.e. no loss of mobility or posture)

	Disease Course		χ^2	P
	Monophasic/Intermediate	Chronic Relapsing		
Presenting feature, n/N (%)				
Severe initial symptoms	16/28 (57)	41/45 (91)	11.6	.001 ^a
Tumor present	8/28 (29)	8/45 (18)	1.2	.28 ^a
Good response to initial treatment	9/27 (33)	16/44 (36)	0.1	.79 ^a
Time interval to treatment, median \pm semi-interquartile range, wk	4.4 \pm 7.0	3.1 \pm 4.0	NA	.21 ^b

Outcome and Prognostic Features in Opsoclonus-Myoclonus Syndrome From Infancy to Adult Life

- Severe initial symptoms 2 times more likely to have learning difficulties
 - Younger age of onset might also predict learning difficulties
- Time from symptom onset to treatment, degree of response to initial treatment, and the tumor status did not affect cognitive outcome.

Outcome measure, n/N (%)	Disease Course		χ^2	P
	Monophasic/Intermediate	Chronic Relapsing		
Motor abnormality/ataxia	6/28 (21)	38/45 (84)	28.6	<.001 ^a
Speech abnormality	12/28 (43)	36/45 (80)	10.5	.001 ^a
Learning disability	5/28 (18)	32/45 (71)	19.5	<.001 ^a
Behavior problems	10/26 (39)	23/31 (74)	7.4	.006 ^a

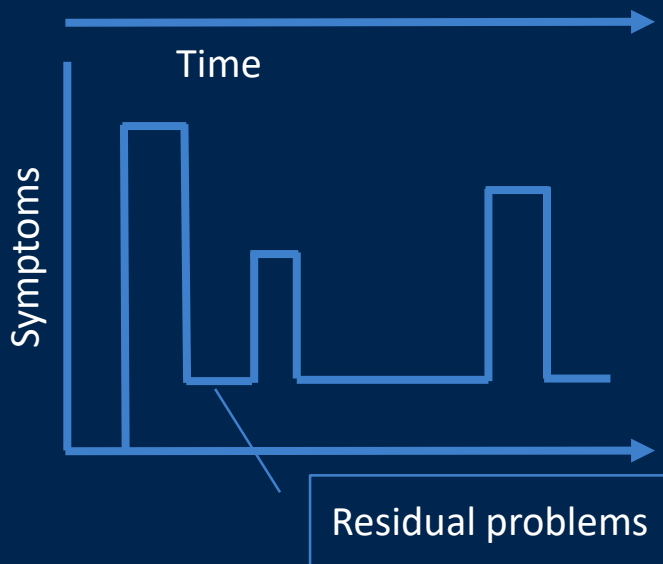
Outcome and Prognostic Features in Opsoclonus-Myoclonus Syndrome From Infancy to Adult Life

- Percentage affected by disabilities did not change across age groups

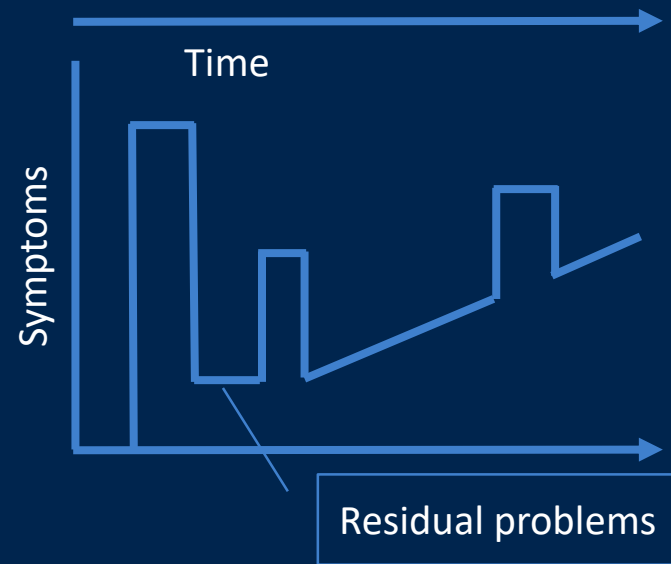
Outcome Measure	Proportion of Patients With Condition per Group, %				χ^2	<i>P</i> ^a
	< 6 y (n = 18)	6-8 y (n = 18)	9-13 y (n = 18)	≥14 y (n = 19)		
Motor abnormality/ataxia	61	67	44	68	2.7	.43
Opsoclonus (intermittent)	6	21	12	21	2.2	.52
Speech abnormality	56	67	72	68	1.2	.74
Learning disability	44	50	50	58	0.6	.87
Behavior problems	47	75	53	60	2.3	.49

OMA does not appear to be a long term progressive encephalopathy

This



NOT
This



Outcome and Prognostic Features in Opsoclonus-Myoclonus Syndrome From Infancy to Adult Life

- Some considerations from this study
 - 2/3 of patients had a range of long-term residual impairments
 - 1/2 had a learning disability
 - 1/3 had normal intellect and cessation of symptoms

Perhaps...

- Triple therapy earlier in disease course, especially for younger and more severe onset might change this outcome

Effect of Increased Immunosuppression on Developmental Outcome of Opsoclonus Myoclonus Syndrome (OMS)

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Abstract


Opsoclonus myoclonus syndrome (OMS) produces long-term cognitive, behavioral, and motor deficits. Objective was to see if more aggressive treatment improved outcome. Assessment included opsoclonus myoclonus syndrome rating, developmental/cognitive and motor assessment, and adaptive behavior. Fourteen subjects completed testing. Nine had neuroblastoma. Onset was at 10 to 35 months; onset to diagnosis: 2 days to 14 months, and onset to first treatment: 5 days to 15 months. Initial treatment was corticotropin (12), oral steroids (3), plus intravenous immunoglobulin in all. Ten received rituximab, 5 cyclophosphamide. Age at testing ranged from 2.5 to 10.3 years. Adaptive Behavior Score (11 subjects), mean 93.5; estimated Intelligence Quotient/Developmental Quotient mean 93.5; Motor: mean 92.8. Residual opsoclonus myoclonus syndrome symptoms at the time of the evaluation were generally minor; opsoclonus myoclonus syndrome scores ranged from 0 to 6. Comparison to previously reported opsoclonus myoclonus syndrome subjects showed improved outcomes: Adaptive behavior, cognitive and motor scores were significantly higher ($P < .001$) in new subjects. Outcomes have improved with more aggressive immunosuppression, with most opsoclonus myoclonus syndrome survivors now functioning at or near normal.

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- Two previous outcome studies: 2002 and 2005
 - 2002 study showed significant neurodevelopmental impairments
 - 2005 study suggested more recently treated patients fared better, perhaps related to evolution of more aggressive treatment
- 15 patients seen over the previous 10 years were compared to an “older” population of OMA patients
 - 9 had NB

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- Interval from onset to diagnosis – 2 days to 14 mo
- Average time of response to initial treatment = 5 weeks (range 1 day to 2 months)
- 13 patients with average of 2 relapses (range 0-4)
 - 2 additional patients did not respond to initial treatment but showed gradual improvement without relapses

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- Treatment differed in that more of the “old” subjects received initial treatment with oral corticosteroids, and fewer received IVIG early in their course.
- None of the “old” subjects received rituximab, compared to 11 of the 15 new subjects.

Table 3. Comparison of Treatment of the Old and New Groups.

Group (n)	Age onset (mo)	Interval to diagnosis (mo)	Interval ≤2 mo (%)	Interval >2 mo (%)	ACTH (n)	Oral steroids (n)	IVIG (n)	Rituximab (n)	Cyclophosphamide (n)	Other ^a (n)
Old (23)	17.19	3.04	57	43	10	13	15	0	2	7
New (15)	17.07	3.14	71	29	12	3	15	11	4	2

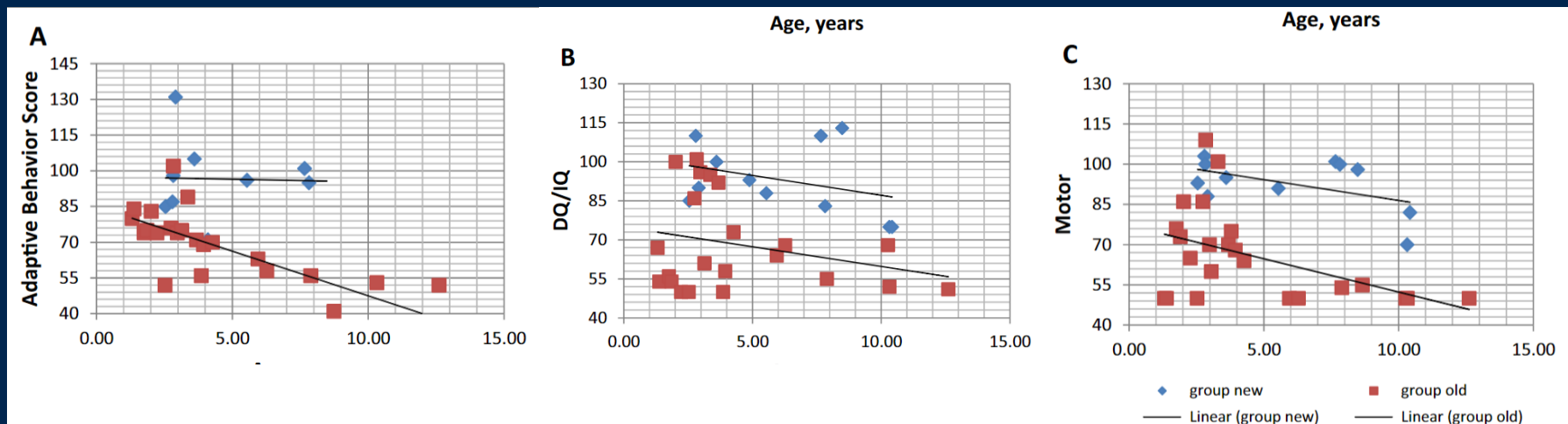
Abbreviations: ACTH, corticotropin; IVIG, intravenous immunoglobulin.

^aOther immunosuppressive medications included azathioprine, mycophenolate, bolus dexamethasone, and autologous bone marrow transplant.

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- New group compared to old group showed improved outcomes




- However, almost all children in new group did still show some mild residual deficits, but still better than old group

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- No differences between new and old subjects in
 - age of presentation
 - duration from first symptoms to diagnosis
 - delay to treatment
 - etiology (neuroblastoma vs no neuroblastoma)
 - tumor histology
 - treatment status at the time of developmental evaluation
 - initial severity symptoms.

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- The major difference was that the new subjects were treated more aggressively
 - Early addition of rituximab, either at time of first relapse or as part of combined initial treatment
 - High dose ACTH or corticosteroids in all, doses increased with even minor signs of relapse
 - Second course of rituximab if relapses occur with steroid taper after recovery of B-cells peripherally (2 recent patients)
 - Cyclophosphamide either initially or if not responding to rituximab
 - Bolus dexamethasone with IVIG if unable to wean fully off chronic steroids

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•Conclusions

- Patients usually respond to initial steroid treatment

But...

Tend to relapse with steroid taper

But...

Long-term steroids have side effects

- “More aggressive” early treatment with third agents such as rituximab may provide improved long term outcomes over single or dual therapy



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Clinical Observations

Opsoclonus-Myoclonus Syndrome: A New Era of Improved Prognosis?



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ABSTRACT

BACKGROUND: Opsoclonus-myoclonus syndrome is an autoimmune neurological disorder characterized by opsoclonus, myoclonus, ataxia, and behavioral changes. Although long-term outcomes have historically been poor, including motor and cognitive disabilities, the advent of new and more aggressive immunotherapy regimens may be improving prognosis in opsoclonus-myoclonus syndrome. **METHODS:** We retrospectively reviewed the records of all children diagnosed with opsoclonus-myoclonus syndrome at BC Children's Hospital from 2000 to 2010. Neurological outcomes were compared with those previously reported in the literature. **RESULTS:** Twelve children with opsoclonus-myoclonus syndrome were identified, four of whom had an associated neuroblastoma. Two thirds of patients received initial treatment with a combination of corticosteroids, intravenous immunoglobulin (IVIG), and an additional immunosuppressant agent. After a median follow-up of three years from diagnosis, ten patients had no or minimal neurological abnormalities. Two patients had poor outcome with significant cognitive impairment. **CONCLUSIONS:** Most patients in this series were treated with early multimodal immunotherapy, and neurological outcomes were better than those in most historical reports. This finding is consistent with recent studies that suggest multimodal immunotherapy regimens may be improving the prognosis in this challenging disease. However, some individuals did well with less aggressive treatment, and further studies are required to determine optimal treatment approach.

Keywords: Opsoclonus-myoclonus syndrome, neuroblastoma, ataxia, immunotherapy

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Opsoclonus-Myoclonus Syndrome: A New Era of Improved Prognosis?

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- Descriptive study of 12 patients followed for an average of 3 years (range 9 months to 11 years)
- 4 patients with NB; 5 post-infectious; 3 unknown cause
- Core OMS symptoms resolved within 2 months on average (range 3 days to 24 months)
- 6 patients had relapses (5 with more than 1)
 - First relapses occurred < 6 months from initial remission and while on treatment (except for 1 pt)
 - 1 of 6 with NB

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- At last follow-up, 8 of 12 = neurologically normal
- 2 patients with “mild neurological difficulties” = poor enunciation and mild coordination problem, respectively
- 2 patients with poor neurological outcome
 - Authors noted longer duration of symptoms before dx of OMA + NB (140 days) in one patient

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- 7 of 8 patients receiving triple therapy (steroid + IVIG + third agent [rituximab, azathioprine]) had good neurological outcome
- 3 of 4 patients with “less aggressive” treatment had good neurological outcome

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• Authors' considerations and conclusions

- More aggressive early therapy might improve outcome
- Earlier recognition might improve outcome

But...

Some patients got better without aggressive therapy and even without any therapy at all

So...

More studies are needed

My personal suppositions

- A more “explosive” presentation of OMA that is either of unknown cause or associated with NB probably needs triple therapy to improve chances for better neurological outcome
- Number and severity of relapses predicts outcomes
- Outcome predicts outcome
 - Recovery and relapses over first 1-2 years predicts outcome

Transition to Transition

Transition and transfer from a pediatric health care system to an adult health care system

I stole this from:

Diane V. Murrell, LCSW

Blue Bird Circle Clinic, Neurology

Texas Children's Hospital



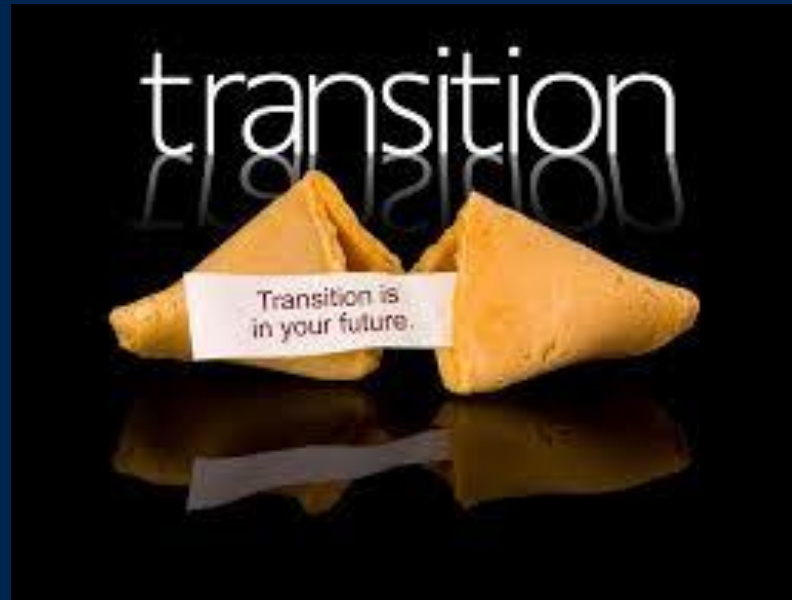
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What's the transition?





Movement, passage, or change from one position, state or stage to another

Eg: the transition from adolescence to adulthood.

What does it feel like to you



Why do

Transition Together



The tasks of ADOLESCENCE

- What other transitions occur during adolescence (13yr – 18yr)

Prescriptions/Obtain? Schedule appointments? Find an adult care doctor ? Type of transportation ? Name of insurance? Will current insurance benefits continue? What are they? New insurance ? Explain diagnosis/ know symptoms when to call ER



How do you juggle everything at once when it is new to you?

Transition readiness

- **Does the patient know their:**

- Medical Condition

- Medications

- Insurance

Does the patient know,

•Medical Condition

- the name of their medical condition & can they explain it to someone else
- the signs that indicate an emergency is approaching
- how to contact their doctor or when to dial 911 & what's an In Case of Emergency (I.C.E) number
- how to schedule their doctor's appointment
- that they must practice speaking to their doctor without their parent in the clinic room

Elevator Speech

THE ELEVATOR PITCH



Does the patient know,

•Medications

- the names of their medications; what they're for; when to take them; & harmful interactions
- how to take medications/treatment on their own
- the dangers of mixing meds with alcohol or other/illicit drugs
- how to fill and refill prescriptions

Does the patient know ,

•Insurance

- the name (s) of their health insurance company
- if their benefits will continue when they transfer to adult-based care, if not , do they know how to obtain insurance
- who is going to be their adult-based doctor, if not, do they know how to find a doctor

How do you order your medical records for transfer?

Printed summary from your doctor(s) to you

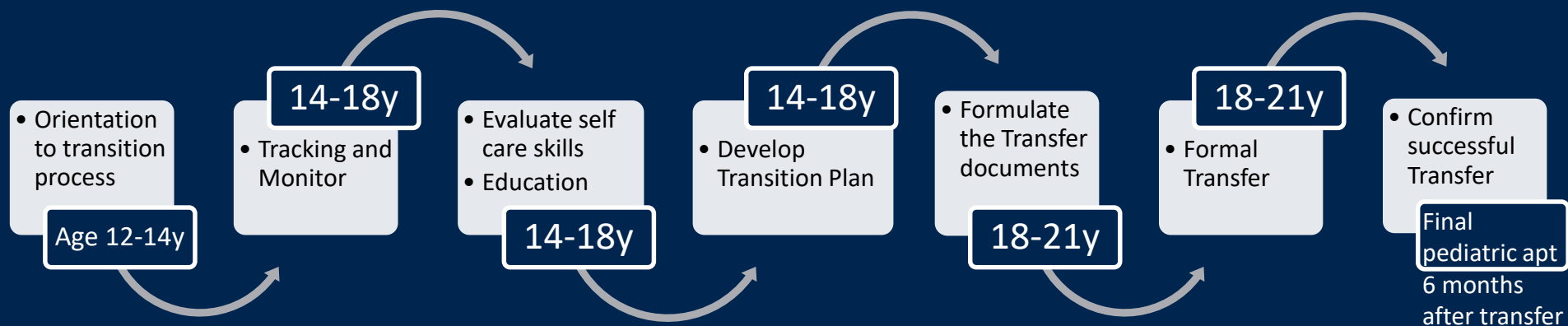
Electronic Medical Record sharing (e.g. Care Everywhere)

Patient can request a "Release of Medical Information" to complete and have their records sent to another provider

Multiple Sclerosis Transition and Transfer

TCH Clinic

Adult
Clinic



Transfer of care targeted toward age 20-21

Barriers for Neurology Transition and Transfer

- Insurance
- Variety of dxes within neurology, difficult to plan generic tools, one size does not fit all
- Lack of adult providers
- Level of parent's education to assist youth and to identify resources relevant to transition
- Language
- Medically complex patients need multiple providers and they
 - a)do not talk with each other
 - b)transition at different times from per service line
- Lack of reimbursement
- Lack of staff, lack of time for Social workers to address psychosocial barriers to successful transition and lack of RNs to help with self management skills related to medications
- Research: natural history studies

Thanks!
OMS Life